CARDIO-RESPIRATORY STUDIES IN ACUTE MYOCARDIAL INFARCTION

by

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SUMMARY

Shock or severe cardiac failure developing in the course of acute myocardial infarction is an ominous event with a grave prognosis. Despite its frequent occurrence, the precise haemodynamic alterations which occur in cardiogenic shock have not been clearly defined. To date there is no uniform agreement about the therapeutic management of these severely ill patients and the widely different therapeutic measures being advocated only emphasise the uncertainty about the precise pathogenesis of shock complicating acute myocardial infarction.

This thesis reviews developments in the concept of myocardial infarction and describes haemodynamic and respiratory studies in patients with acute myocardial infarction.

The investigations show that nearly all patients with recent myocardial infarction have abnormal cardio-respiratory function. Even in patients with so called 'uncomplicated' myocardial infarction, cardiac output is in the low normal range and the mixed venous oxygen saturation is reduced. A number of these patients have a raised pulmonary arterial pressure. Mismatching of ventilation and perfusion results in arterial hypoxia. The clinical diagnosis of left ventricular failure is not always easy and the abnormal cardio-respiratory function suggests that sub-clinical left ventricular failure is a relatively common finding in acute

myocardial infarction.

In patients with cardiogenic shock or clinical left ventricular failure, the disorders of cardiac and pulmonary function are more marked but the similarity of the abnormalities suggests that left ventricular failure is present in both groups. The finding of raised pulmonary arterial pressures in the patients with cardiogenic shock is in accord with this view. In general the more severely ill the patient the greater is the degree of cardiac failure and respiratory abnormality.

The thesis also documents attempts to treat the impaired left ventricular function in cardiogenic shock by digitalis and acid-base correction and comments on the failure of this approach.

The failure to alter the course of cardiogenic shock by pharmacological agents is similar to the reports of many other investigators. Pain and anxiety are present in many of these patients and this can be relieved by opiates, but recent reports have suggested that morphine can produce marked hypotension in patients with acute myocardial infarction and that morphine should be used with great caution, if at all. A detailed examination of the circulatory effects of morphine and heroin in myocardial infarction is presented. The results suggest that morphine is a suitable analgesic for the relief of pain in acute myocardial infarction.

INTRODUCTION

Intensive care and therapy units are now well established in the management of acute myocardial infarction. They do reduce the mortality from serious arrhythmias, possibly by prevention, but certainly by effective therapy. However, the improved management of arrhythmias has focussed attention on the major remaining problem, that of shock and severe heart failure complicating acute myocardial infarction.

Of the first 400 cases of myocardial infarction admitted to the Coronary Care Unit of the Royal Infirmary of Edinburgh, there were 70 deaths (17.5%). 32 of these deaths occurred in patients who were graded as being shocked and 9 deaths occurred in patients with persistent failure. (Lawrie, Greenwood, Goddard, Harvey, Donald, Julian and Oliver, 1967) (Oliver, Julian and Donald, 1967). Thus the majority of deaths in patients with myocardial infarction admitted to hospital occurred in patients with shock or severe failure. If there is to be further improvement in the care of acute myocardial infarction, a major area of concern must be in the understanding of the mechanism of shock and failure complicating this condition so that a rational therapeutic approach can be planned.

Acute myocardial infarction is frequently followed by a fall in blood pressure and in a number of patients this is associated with the clinical signs of shock. The proportion of patients in whom this complication arises, has varied widely from one centre to

another because of varying criteria for the definition of shock. In general when the criteria are stringent, the incidence of shock is lower and the mortality higher. Freidberg (1961) reviewed the incidence of shock in 2,955 cases of acute myocardial infarction in 10 reported series and noted the incidence to be 14% with a mortality of 79% when strict criteria were applied, but 52% incidence with a 36% mortality when the less strict criteria were used. The use of inadequate criteria for the diagnosis of cardiogenic shock has led to many therapeutic claims which have not been confirmed by subsequent workers. Strict criteria are essential if therapeutic results are to be compared between different centres.

In the Coronary Care Unit of the Royal Infirmary of Edinburgh, we have continued to use the criteria described by MacKenzie in 1965. His diagnosis of cardiogenic shock was based on the findings of a systolic blood pressure on auscultation of less than 100 mm Hg in the presence of cold, clammy, sweating and cyanosed extremities with associated clouding of consciousness, usually manifested as mental apathy or restlessness. Using such criteria the incidence of shock in the Coronary Care Unit of the Royal Infirmary of Edinburgh was 9% of admissions with acute myocardial infarction and the mortality in this group was 83% (Lawrie et al., 1967). The incidence and mortality pattern suggest that such diagnostic features provide stringent criteria for defining shock.

Nevertheless, the criteria are largely subjective and there is a great need to find a relatively simple objective measurement of the patient's circulatory state to aid in the clinical assessment and to provide documentation about claimed therapeutic success.

In the treatment of cardiogenic shock, various therapeutic measures such as intravenous transfusion, intra-arterial transfusion, cardiac glycosides, vasopressors, vasodilators and assisted circulation have been suggested. To date there is no uniform agreement about therapeutic management thus emphasising the wide divergences of opinion regarding the pathogenesis of shock complicating acute myocardial infarction.

This thesis is presented as an account of the cardio-respiratory status of patients with varying grades of severity of acute myocardial infarction and describes the abnormal physiology of shock in relation to that of other patients with myocardial infarction without shock. It documents therapeutic manouevres which were carried out to treat the patients with cardiogenic shock and an examination of their response to such therapy, gives additional information about the patho-physiology of this condition. Cardiogenic shock was a term used by Harrison (1935) to describe shock occurring in a variety of conditions of shock in which the heart might be implicated. Most workers restrict the term to shock complicating acute myocardial infarction, but confusion about pathogenesis and therapy still exist because some of the claims for

therapeutic success have been documented in other types of shock, particularly the low output state following cardio-pulmonary bypass (Dietzman and Lillehei, 1968). In this thesis the term cardiogenic shock will be restricted to shock complicating acute myocardial infarction; furthermore as shock may complicate arrhythmias and be reversed following the successful treatment of the arrhythmia, the term cardiogenic shock will be reserved for those patients in basically sinus rhythm.

The thesis is presented in six chapters. Chapter I is a review of developments in concepts of myocardial infarction. Also considered are studies of altered physiology in acute myocardial infarction with particular reference to patients who are judged clinically to be severely ill. In Chapter II there is a general outline of techniques and investigational methods used in the work reported in this thesis. Each of the remaining chapters will report the results of studies and will present relevant discussion. Chapter III will present detailed results of circulatory and respiratory studies in acute myocardial infarction of varying grades of severity. Chapter IV will report the results of therapy with digoxin, acid-base correction and volume loading in patients with cardiogenic shock.

There is often only a poor response to therapy in severe grades of acute myocardial infarction. Opiates do provide relief of pain but a report by Thomas, Malmcrona, Fillmore and Shillingford (1965) suggested that the traditional regime of morphine could

produce marked hypotension and that morphine should be used with great caution if at all. Chapter V describes the circulatory effects of morphine in patients with acute myocardial infarction and compares these effects with previously published results on the circulatory effects of heroin (MacDonald, Rees, Muir, Lawrie, Burton and Donald, 1967).

As the comparison showed little real difference between the two opiates and was in conflict with the report of Thomas and his colleagues, a second more detailed comparison of these two opiates was made using a randomised patient allocation, a 'blind' administration schedule and newer and more sensitive statistical techniques. This study is reported in Chapter VI.

The main conclusions and recommendations concerning the management of patients with shock complicating myocardial infarction are contained in the final summary.

DEVELOPMENTS IN THE CONCEPTS OF MYOCARDIAL INFARCTION

CHAPTER I

Although coronary artery disease has become one of the major diseases of the 20th Century, it is difficult to be certain whether this disease was prevalent in earlier times. Chest pain is mentioned by William Harvey in a letter to Riolan (1649) when he described "a man who did often complain of an oppression in his breast" - "at last opprest in a signal paroxism he died". However, the autopsy showed aortic stenosis and a rupture of a large left ventricle. There must also be doubt about the role of coronary artery disease in a case described by Giovanni Maria Lancisi who, whilst investigating the causes of sudden death in Rome in 1707, noted one "obese gouty,plethoric person" with praecordial pain who died at a meal. Autopsy showed a pericardial sac full of blood from the rupture of an aneurysm. Lancisi quoted Hippocrates as saying "pain in the heart coming rather often means sudden death". Neither Harvey nor Lancisi attributed the pain to disease of the coronary arteries.

Studies in palaeopathology also fail to determine whether coronary artery disease occurred in earlier centuries. Atheroma in the aorta has been noted in mummies from all Egyptian dynasties (Ruffer 1921) but there are no accounts of pathology in the coronary arteries. Contrary to the view of Oliver (1954) this is not because the heart was removed at the time of mummification. The ancient Egyptians believed the heart was the seat of the soul and in nearly all dynasties the heart was thrust back into the thoracic cavity at

the time of evisceration. Mummification was inadequate to preserve the heart and coronary arteries (Ruffer 1921).

The history of coronary artery disease probably starts with Heberden's precise account of the symptomatology of angina pectoris to the College of Physicians in London in 1768. Heberden had not linked the anginal pain with coronary artery disease; this relationship was first mentioned by Jenner but he delayed publication for fear of alarming John Hunter, in whom he had diagnosed angina pectoris (Bedford 1968). By 1799 Parry had published his "Inquiry into Syncope Anginosa" and this coronary theory was also supported by Burns in his text book on heart disease (1809).

Over the next 100 years the recognition of coronary heart disease became obscured by a number of controversies and under Laennec's influence the concept of fatty degeneration of the heart was widely held to be the cause of chest pain. It was not until the end of the 19th Century that Weigert (1880) and Zeigler (1881) established the ischaemic basis of acute infarction and fibrosis and related them to coronary occlusion. Despite confusion about the aetiology of anginal pain during the 19th Century in the medical literature, ideas about the course of the disease had permeated lay literature. George Eliot in 'Middlemarch' made Dr. Lydgate say to Mr. Casaubon 'My conclusions are doubly uncertain; uncertain not only because of my own fallibility but because diseases of the heart are eminently difficult to form predictions on. I believe you are

suffering from what is called fatty degeneration of the heart..... It is my duty to inform you that death from this condition is often sudden. At the same time no such result can be predicted. Your condition may be consistent with a tolerably comfortable life for another fifteen years or more".

By the end of the 19th Century the concept of coronary artery disease as a major cause of illness was being discussed. Gibson and Muir (1894) reported a case of cardiac fibrosis as a result of coronary obstruction in a patient admitted to Ward 22 of the Royal Infirmary, Edinburgh. In the discussion of their paper they drew attention to the presence of praecordial pain and at autopsy "to the narrowing of the coronary arteries which become obliterated or thrombosed and cause infarction of the heart wall - soft necrosed areas which form the condition known as myomalacia cordis".

The most complete early description of the syndrome of myocardial infarction was not until Herrick's paper of 1912. The widespread recognition of the disease followed Herrick's second paper in 1918 and Pardee's description of electrocardio-graphic changes in 1920. The first large series of cases was reported by Levine and Brown in 1929 in an extensive paper in which they analysed the clinical features of 145 cases of coronary thrombosis and pathological data of 46 of these. Their main conclusions were that angina pectoris generally precedes attacks of coronary thrombosis but in some cases there was no history of angina nor of any other pre-existing disease. They showed that coronary thrombosis was common in diabetics and also noted transient glycosuria in many patients at the

time of infarction. Hypertension was often a pre-existing disease. They drew attention to the distribution of the pain, the fever and leucocytosis and to physical signs of pericardial friction rub and râles in the lungs. Whilst discussing modes of death they described patients who have "general failure of the circulation.....Here the shock to the circulation is sufficient to depress the blood pressure to very low levels such as 60 or 80 mm, or the pulse may be imperceptible. The patient then presents the picture of profound shock and may be actually unconscious".

The first study of circulatory dynamics in myocardial infarction was reported by Fishberg, Hitzig and King (1934). They studied venous pressure, measured peripherally, circulation time measured as arm to tongue time and volume of circulating blood using congo red in 59 patients. In all cases of massive infarction they noted the clinical features of shock which they described as: greyish acrocyanois, cold extremities, moist skin, superficial respiration which may or may not be rapid, but no orthopnoea; collapsed superfical veins and a pulse which is often most rapid, small and of low tension. They recorded that these shocked patients had low venous pressures and a low circulating blood volume. The very nature of their investigative techniques must cast some doubt on their findings but it is curious that their conclusions that cardiac failure and shock in myocardial infarction operate from differing mechanisms one from circulatory overload and one from volume depletion,

is an argument that still divides clinicians treating patients with acute myocardial infarction. Fishberg modified his views later when he stated that the clinical picture of shock in myocardial infarction was the result of a marked decrease in cardiac output from acute myocardial failure (Fishberg 1940). Such a view was also held by Stead and Ebert (1942). In a study of venous pressure, arm to tongue circulation time and plasma volume measured by Evans blue, in cardiogenic shock, they observed that despite the absence of dyspnoea and in the presence of low venous pressures the chest x-ray always showed pulmonary congestion. However, the plasma volume was slightly smaller than predicted volumes. In 2 subjects venesection of 500 c.c. of blood caused neither clinical improvement nor a change for the worse. They concluded that there was imbalance of the circulation and that because of infarction of muscle the heart was unable to respond to Starling's law of the heart.

Cardiac output in acute myocardial infarction was first measured by Grishman and Master (1941) using the Wezler-Boeger method based on analysis of the pulse pressure and pulse wave velocity. They recorded cardiac outputs ranging from 3.15 to 5.9 litres/min in 5 patients with infarction but without shock. Starr and Wood (1943) also studied cardiac output in patients with infarction but their technique was that of ballisto-cardiography. They concluded that in acute infarction, cardiac output was either normal or below normal but not as low as that of patients who suffered from

angina pectoris.

In 1950 Pritchard and Hellerstein reported the results of cardiac outputs determined by the Fick method in 11 patients with acute myocardial infarction but without shock; cardiac outputs were in the lower ranges of normal. To calculate the arteriovenous oxygen difference, they sampled venous blood from the great veins; oxygen sampling from a central vein has been criticised as an inadequate guide to true mixed venous blood oxygenation (MacKenzie 1965). Recently Scheinman, Brown and Rapaport (1969) showed that venous oxygen saturations collected from atrial level correlated quite well with pulmonary arterial blood in patients with uncomplicated myocardial infarction, but in patients who were severely ill with failure or shock the correlation between saturations from the great veins and the pulmonary artery was much less close. As the patients studied by Hellerstein and Pritchard were in the uncomplicated group, their output determinations may not have been seriously in error.

The first comprehensive circulatory investigation of acute myocardial infarction was reported by Freis, Schnapper, Johnson and Schreiner (1952). They studied 11 patients, 4 of whom were uncomplicated, 5 were moderately severe or severe and 4 had the features of shock. The 5 moderately severe or severe had clinical features of left ventricular failure. Arterial pressure was measured intravascularly from the femoral artery and cardiac output was measured with a dye dilution technique using Evans blue (T 1824)

as an indicator. Their results are summarised in table I and showed that the more severe the infarction the lower was the cardiac output and stroke volume. The authors suggested that the primary event in cardiogenic shock was a reduction in left ventricular output.

Smith, Wikler and Fox (1954) reported a similar study in which they had examined the circulatory status of 10 patients without shock and 9 patients with shock. Cardiac output was measured by the indicator dilution technique with intermittent arterial sampling, but whereas Freis and colleagues had injected dye into the great veins in the study of Smith, Wikler and Fox the dye (T 1824) was injected into the femoral vein or antecubital vein. The possible 'peripheral trapping' of dye with forearm injection increases the error in dye dilution estimations of cardiac output. The point is of some importance as the findings of Smith and colleagues suggested that cardiac output was equally low in patients without evidence of shock and that the reduction in cardiac output was only one of the features that determined the clinical appearance of the patient. Blood volume studies revealed no significant deviation from the normal.

Gilbert, Goldberg and Griffin (1954) and Gammil, Applegarth, Reed, Fernald and Antenucci (1955) reported on the haemodynamic features in acute myocardial infarction. Cardiac output determinations were again made by intermittent arterial sampling of peripherally injected dye. Both groups concluded that the degree of reduction of cardiac output was roughly proportional to the clinical severity of

the attack. Despite the observations by Freis et al. (1952) of the surprisingly large differences between blood pressure measured intra-arterially and by sphygmomanometry, Gammil and colleagues measured blood pressure by sphygmomanometer.

There were further reports of haemodynamics in myocardial infarction by Lee (1957), Broch, Humerfelt, Haarstad and Mylvie (1959) and Murphy, Glick, Schreiner and Yu (1963) (Table I). These reports tended to confirm the findings of low cardiac output in the severely ill. Lee's study merits special comment. He studied 11 patients whom he graded arbitarily in clinical severity 0-4. Grade 0 represented uncomplicated myocardial infarction and grade 4 the full shock syndrome. Only 1 patient fell into grade 4, but 4 patients were in grade 3, with most of the features of shock. Cardiac output was measured using a dye dilution technique with T 1824 as an indicator and the dilution curve was obtained by intermittent arterial sampling. His measured cardiac outputs corrected for body surface area were higher than others had recorded, but were reduced in patients who were severely ill. Central venous pressures were elevated and forearm blood flow was approximately half normal. He also recorded that there was no overshoot to the Valsalva manoeuvre in the most severely ill. He noted the apparent paradox that despite circulatory evidence of heart failure clinical signs of pulmonary oedema were absent or slight. He evoked a "Bernheim" effect with pressure from the left ventricle impairing right ventricular function and resulting

in some sparing of the pulmonary system in spite of a failing left ventricle.

MacKenzie, Taylor, Flenley, MacDonald, Staunton and Donald (1964) and MacKenzie (1965) working from the Department of Medicine of the Royal Infirmary, Edinburgh, described a series of 9 patients with uncomplicated myocardial infarction, 2 patients with left ventricular failure and 6 patients with cardiogenic shock. In a detailed and careful study they confirmed the earlier observations of reduction of cardiac output in the severely ill, but again noted that equally low values were found in some cases of myocardial infarction without shock. There was no such overlap in stroke volume and they suggested that in cardiogenic shock, patients were sometimes able to maintain cardiac output by an increase in heart rate. Patients with shock had high right atrial pressures. Such a reduction in stroke volume in the absence of apparent hypovolaemia suggested a severe impairment of left ventricular function. MacKenzie (1965) also showed a reduction of various measurements of myocardial performance such as maximum rate of pressure rise in the aorta, mean ejection-flow index and stroke-power index implicating failure of the left ventricle as a pump.

In addition MacKenzie and his colleagues drew attention to the arterial hypoxia that existed in the shocked patients and that the administration of oxygen failed to cause a normal increase in arterial oxygen tension. From his calculations approximately 25% of the

blood was being shunted through the lungs without coming into contact with gas exchanging units in patients with cardiogenic shock. These patients also exhibited a marked metabolic acidosis with lacticacidaemia. MacKenzie postulated that this severe metabolic acidosis might cause a reduction in myocardial contractility and also cause a refractoriness to the action of drugs such as digitalis. As the current study was conducted using the same diagnostic criteria and similar equipment and techniques as those used by MacKenzie and his colleagues the haemodynamic data from their study will be presented along with the data from the present investigation.

Following the observations of MacKenzie et al. (1964) there were a number of reports of blood gas changes and pulmonary function in acute myocardial infarction. McNicol, Kirby, Bhoola, Everest and Freedman (1965) divided their patients into 4 groups. Group I consisted of 14 patients with uncomplicated myocardial infarction, in group 2 there were 2 patients with myocardial infarction and shock, the 13 patients in group 3 had shock and pulmonary congestion and in group 4 there were 44 patients with myocardial infarction and pulmonary congestion. They found arterial hypoxaemia in all patients with pulmonary congestion. In contrast to the findings of MacKenzie and colleagues (1964), they found it was possible to influence the hypoxia of shock not only by oxygen therapy but also by diuretics. They concluded that the arterial hypoxaemia was due to severe ventilation perfusion imbalance and that the more severe the hypoxia,

the more likely it was to be relieved. In a further paper from the same group (Kirby and McNicol, 1966) they confirmed the finding of a severe metabolic acidosis in the more severely ill. As they presented no haemodynamic studies and their clinical groupings were not the same as used by previous workers (Freis, et al. 1952, MacKenzie et al. 1964), their data is not strictly comparable with the studies of MacKenzie and colleagues, nevertheless their studies provided useful confirmatory evidence of the hypoxaemia and metabolic acidosis in severely ill patients.

Blood gas changes after acute myocardial infarction were also reported by Valentine, Fluck, Mounsey, Reid, Shillingford and Steiner (1966). They again confirmed the arterial hypoxia in patients with acute myocardial infarction and by measuring mixed venous blood were able to show reduction of venous oxygen saturation in all patients. All their patients had an increase alveolar to arterial oxygen gradient and venous admixture (Qva) was increased. However, after oxygen breathing in 7 patients there was an increase in arterial oxygen tension to greater than 396 mm.Hg in all patients and therefore the "true shunt" (Qs) was small. The patients studied were not seriously ill and their observations do not conflict with those of MacKenzie (1965).

A further study of factors influencing pulmonary gas exchange during the acute stages of myocardial infarction was reported by Higgs (1968). She studied 17 male patients during the acute stage

and found the dead space to tidal volume ratio (Vd/Vt) was increased and that the arterial oxygen tension was reduced in all patients. Venous admixture was greater than normal both when air or 100 oxygen was breathed. In the presence of pulmonary congestion, venous admixture was as great as 50% when breathing air and fell to 20% whilst breathing oxygen. An imposed increase in tidal volume while breathing air decreased the abnormal Vd/Vt and increased the arterial oxygen tension. These results showed the hypoxaemia to be due to a combination of ventilation perfusion imbalance and intra-pulmonary shunting presumably past groups of atelectatic alveoli or those filled with oedema fluid. The abnormalities were greatest in patients with pulmonary congestion. Similar findings were reported by Pain, Stannard and Sloman (1967) who emphasised that not all of the ventilatory disturbance was due to an imbalance of ventilation and perfusion but that in some patients there was quite marked veno-arterial shunting.

Right heart pressures in acute myocardial infarction were reported by MacDonald, Rees, Muir, Lawrie, Burton and Donald (1967) in a report on the circulatory effects of heroin. One patient with shock and left ventricular failure had a high mean pulmonary arterial pressure (38 mm Hg). A larger series of cases (26 patients) was reported by Fluck, Valentine, Treister, Higgs, Reid, Steiner and Mounsey (1957). A raised systolic pulmonary arterial pressure was found in 21 patients. This pressure returned to normal by the end of a week in all but 3 patients who remained in left ventricular

failure. Radiological evidence of pulmonary oedema was seen in 9 patients in all of whom pulmonary arterial pressure was raised on admission. These patients had the greatest reduction in arterial oxygen tension. The authors did not attempt to classify their patients but analysis of their results indicates that few of their patients were severely ill and no patient was shocked.

Following the observations of arterial hypoxaemia in acute myocardial infarction there were a number of studies of the effects of oxygen therapy. MacKenzie et al. (1964) had noted that oxygen administration in patients with uncomplicated myocardial infarction caused a slight reduction in heart rate and cardiac output but an increase in arterial blood pressure and systemic vascular resistance. In patients with cardiogenic shock, there was a variable response to oxygen therapy although in 1 patient cardiac output and systemic arterial pressure were increased by significant amounts. The abnormally low arterial oxygen tensions obtained breathing 100% oxygen in these patients have already been noted. Cameron, Hutton, Kenmure and Murdoch (1966) reported on the haemodynamic and metabolic effects of hyperbaric oxygen in myocardial infarction, 2 of their patients fit the clinical description of shock. Cardiac output was measured using an ear-piece technique. In the 2 shocked patients, cardiac outputs were low, arterial hypoxia was present and arterial blood lactates were elevated. After therapy with oxygen at 2 atmospheres hypoxia was relieved and blood lactates were reduced but not

to normal levels. However, oxygen therapy at 2 atmospheres did not seem to influence the eventual outcome.

Foster, Casten, Reeves and Hurst (1969) studied the effects of oxygen breathing in 13 patients with myocardial infarction without failure or shock. The patients breathed 4 different levels of inspired oxygen (20.8%, 47.1%, 60.4% and 73.5%) and changes in haemodynamics and the chemical and blood gas responses to oxygen were noted. They compared their findings with the responses of a group of normal subjects. The patients with infarction had a lower mean arterial oxygen tension which did not rise as high as did the normal subjects with increasing concentrations of inspired oxygen. The patients with a lower cardiac output had a lower arterial oxygen tension than patients with high cardiac outputs. There was an increase in peripheral resistance and blood pressure with increasing concentrations of oxygen in inspired air. They noted a decline in lactate and pyruvate levels over the duration of the study and concluded that oxygen therapy apparently increases the oxygen available at the peripheral tissues, but increases the work of the heart by raising peripheral resistance. However, the recorded lactate levels were low and even the highest mean level which occurred in the patients with low outputs (mean lactate 1.376 m.M./L. blood water, mean pyruvate 0.118 m.M./L. blood water) was not significantly greater than the values obtained in the normal subjects. Significant lactic acidaemia could not be said to be present in any

of their patients. It is of interest that while the central venous pressure was higher in the patients than in the normal subjects, the patients with the lower cardiac outputs had significantly lower central venous pressures than did patients with the higher cardiac outputs.

There were further circulatory studies in shock complicating acute myocardial infarction by Gunnar, Cruz, Boswell, Co, Pietras and Tobin (1966) who studied 23 patients, 12 of whom were shocked. The clinical criteria for shock were well defined and similar to those used by MacKenzie et al. (1964). They confirmed the findings of a low cardiac output in cardiogenic shock and showed that peripheral vascular resistance could be either high or low. Examination of their data suggests that this finding is entirely explicable on their differing cardiac outputs as there was little difference in arterial pressure in all patients. They found that peripheral resistance could be increased in most patients by vasopressor therapy, but that cardiac output then fell. In 2 patients systemic vascular resistance was not increased by vasopressor therapy and they postulated that these 2 patients had vasomotor unresponsiveness, perhaps due to acidosis, but made no measurement of the acid-base status of their patients.

In a study from McGill University, Smith, Oriol, Morch and McGregor (1967) studied the effects of treatment with isoproterenol (isoprenaline) and metaraminol in 14 patients with shock complicating

acute myocardial infarction. They documented normal values for peripheral resistance and interpreted their findings as reflecting acute heart failure, in association with a peripheral vascular response that was inadequate to maintain normal blood pressure (Table II). Isoproterenol caused a decrease in venous pressure and an increase in cardiac output, this usually caused an increase in blood pressure but in a few patients the inotropic effects of the drug were less than its peripheral action and caused a fall in blood pressure. Metaraminol caused elevation of blood pressure at the expense of a fall in cardiac output. Comment about the acid-base status of their patients is pertinent. They measured pH in 9 of their 14 patients and this was greater than 7.37 in 4 of these 9 patients. A summary of their haemodynamic data and the data of Gunnar and colleagues is presented in Table II.

In calculating systemic vascular resistance, MacKenzie and colleagues had incorporated an allowance for central venous pressure giving the so-called driving pressure.

Thus:

$$SVR = \frac{\text{Mean Aortic Pressure - Central Venous Pressure}}{\text{Cardiac Index}} \times 0.7994$$

$$\text{dynes.sec.cm}^{-5}\text{m}^{2}$$

A similar equation was used by Gunnar's group and in the study by Smith and his colleagues. Resistance is the pressure drop (P_1-P_2) along the segment related to volume flow and as such venous pressure can be equated with P_2. This is valid if the system behaves as a

rigid tube and then resistance would be proportional to flow. In living elastic vessels, the relationship is only approximate. A certain threshold pressure is required to start flow, which then increases rapidly as the vessel expands, finally the vessel resists further stretching and increase in flow levels off with further increase in pressure (Kitchin and Julian 1968). The threshold value of pressure below which flow stops is the critical closing pressure. Weil and Shubin (1968) emphasised the importance of this critical closing pressure (Clp) in the calculation of peripheral resistance as there is no arterial flow until this closing pressure is exceeded and suggested that the equation for resistance would be more properly rewritten:

$$\text{Resistance} = \frac{\text{Pressure} - \text{Clp}}{\text{Flow}}$$

However, once critical closing pressures have been exceeded, the relationship pressure to flow does become approximately linear. Absolute values of critical closing pressures are not known although typical values would be between 25 and 40 mm Hg (Burton, 1954, Burton, 1965). Permutt and Riley (1963) have presented a detailed theoretical analysis of critical closing pressure in relation to vascular tone.

There are further problems in the interpretation of calculated systemic vascular resistance; changes in the ratio of pressure to flow are not necessarily attributed to changes in arterial tone, nor does such a ratio provide information about changes in regional vascular beds. In addition, the numerical value for resistance is no better than the measurements on which it is made.

The McGill group (Smith et al. 1967 and Sekelj and Oriol 1967) have pointed out difficulties in the interpretation of dye dilution curves in low output states. The precise point of recirculation is difficult to define in the long drawn-out dilution curves. The Hamilton technique may be in error if recirculation occurs early in the downslope. Smith et al. (1967) advocated use of the Dow formula which is based on measurement of the forward area of the curve only, but this method is in general less accurate than the Hamilton technique and even the Dow formula could be in error in very low output states if recirculation occurred on the upslope. Some of these difficulties can be overcome by central injection but it is likely that alternative techniques such as thermal dilution, in which recirculation is unimportant, will prove more useful in the study and management of low output states.

Measurements of pressure are less likely to be in error. However, measurement from differing sites such as aorta and radial artery will cause variation in pressures obtained (McDonald 1960).

Because of these considerations, systemic vascular resistance is best regarded as a simple ratio and precise interpretations from this ratio should be made with caution.

In an attempt to find either a single factor or a number of factors which might be combined and considered as a single index to quantitate the patient's condition, Shubin, Afifi, Rand and Weil (1968) examined a number of haemodynamic features in 20 patients

who they described as having the "unequivocal clinical manifestations of shock". They carried out a detailed haemodynamic study in patients with acute myocardial infarction and correlated their findings in those patients who survived (6) and those who died (14). The relative importance of individual and groups of haemodynamic parameters was assessed using discriminate function analysis. They found individual measurements of stroke index or cardiac index were more reliable than measurements of blood pressure as indicators of survival. The discriminant function or its equivalent, the probability of survival, served as an indicator of the severity of shock. Although they made no measurements of acid-base status or hypoxia, they suggested that such measurements could be incorporated into the discriminant function analysis and provide greater information and accuracy. They also pointed out that this technique might provide an objective basis for assessing the effectiveness of drug therapy. Their results are summarised in Table 2; group IIIa represent the survivors, IIIb the non-survivors.

Most studies then have shown low cardiac outputs and high venous pressures in cardiogenic shock and it seemed likely that patients with shock represented the far end of a spectrum of left ventricular failure as a response to infarction. The disturbances in pulmonary function were in keeping with this hypothesis.

Doubt on this was again cast by the clinical reports of

Nixon and his colleagues (1966, 1967 and 1968 a, b, c) demonstrating that patients with cardiogenic shock could be improved by infusion of dextrose. Moreover they made direct measurements of left atrial pressure in 1 patient and showed this to be normal (Nixon, Taylor and Morton, 1968). That volume depletion existed in cardiogenic shock was also suggested by Swan, Danzig, Sukumalchantra and Allen (1969) who treated 32 patients with volume expansion, 12 of whom had a favourable response as judged by an increase in urine flow and blood pressure. No haemodynamic studies were performed and no details of their patients were published. The same group had communicated this information in abstract form previously (Allen, Danzig and Swan, 1967, Allen, Danzig and Swan, 1968).

Loeb, Pietras, Tobin and Gunnar (1969) reported a more detailed study in which they treated 12 patients with the clinical features of shock following acute myocardial infarction with low molecular weight dextran (LMWD) used as a plasma expander. In 10 of the patients, central venous pressure was less than 7 mm.Hg (zero reference point not stated). In the remaining 2 patients, central venous pressure was 10.5 and 12 mm.Hg. These 2 patients did not respond to LMWD. They divided the remainder of their patients into 2 groups depending on their response to LMWD. 5 patients showed marked clinical improvement and increased urine flow after volume expansion. These patients all survived their illness. A study of their haemodynamic status prior to therapy

shows that this group had a mean arterial pressure of 68 ± 10 mm.Hg whilst the non-survivors had a mean arterial pressure of 78 ± 15 mm Hg. Cardiac index also showed considerable difference, the surviving group had a mean cardiac index of 2.9 ± 0.8 $l.min.m^2$ whilst the non-survivors had a mean cardiac index of 2.2 ± 0.8. The cardiac index was increased in both groups after treatment with low molecular weight dextran but the high values of cardiac outputs and the absence of other haemodynamic and metabolic data must cast doubt on the clinical classification of the patients.

Clarke, Deegan and McKendrick (1968) had reported to the British Cardiac Society a study of blood volume changes in acute myocardial infarction. They used ^{131}I labelled albumin as an indicator. Patients with uncomplicated infarction showed a slightly reduced blood volume. Blood volume was increased in left ventricular failure, but in 3 patients with shock the blood volume was considerably reduced. The principle of blood volume measurements is to label a sample of plasma or red cells with a distinctive measurable substance. After an adequate time to ensure adequate mixing the extent of dilution is taken to represent the volume of plasma or red cells (Lewis and Szur, 1967). However, if there is inadequate mixing time or there is peripheral pooling of blood, conditions very likely to occur in shock, then the dilution will be unrepresentative and will lead to erroneous estimates of blood volume.

Kirby, McNicol and Tattersfield (1968) reported haemodynamic findings including left ventricular pressure in two patients with severe myocardial infarction with some of the clinical features of shock. One patient had a normal cardiac output with a right atrial pressure of 12 mm.Hg and a mean pulmonary arterial pressure of 31 mm.Hg. In this patient, left ventricular end-diatolic pressure was 23 mm.Hg. This patient had a pH of 7.44 and a plasma-bicarbonate of 26 mequiv.litre. The second patient had a metabolic acidosis (pH 7.37, plasma-bicarbonate 13.5 mequiv.litre) and a low cardiac output; right atrial pressure was 17 mm.Hg, right ventricular pressure 39 mm.Hg systolic, 17 mm.Hg end-diatolic and left ventricular end-diastolic pressure 33 mm.Hg. In these 2 patients then there was unequivocal evidence of left ventricular failure and no suggestion of volume depletion.

Cohn, Khatri and Hamosh (1969) reported in abstract form measurement of left ventricular end-diastolic pressure (LVEDP) in patients with shock complicating acute myocardial infarction and noted that LVEDP was raised in all patients even when right atrial pressure was normal. No further details were given.

Russel, Rackley, Pombo, Hunt and Dodge (1969) also reported in abstract form measurement of left ventricular pressures in acute myocardial infarction. No mention was made of the clinical state of the patients. Left ventricular filling pressure ranged from 3 to 22 mm.Hg. They infused low molecular weight dextran and studied

the changes in stroke volume. They increased left ventricular filling pressures from 9 to 36 mm Hg, but stroke volume only increased with pressure increments up to 20 mm Hg. They concluded that one could expect little increase in cardiac output by elevating filling pressures above 20 mm Hg. In the absence of clinical data about patient selection these studies do not provide further information about the presence or absence of volume depletion in cardiogenic shock.

If volume depletion played a significant role in cardiogenic shock, it might be expected that post-mortem studies would reveal a number of patients dying with relatively small infarcts. This was implied by Nixon, Ikram and Morton (1966) and had been the subject of a study by Kurland, Weingarten and Pitt (1965). They studied the post-mortem and clinical data of 127 patients dying of acute myocardial infarction and tried to correlate the relationship between primary branch occlusions and cardiogenic shock. The relative frequency of shock was significantly greater in patients with branch occlusions, and branch occlusions were associated with extensive infarction. It is interesting to note that although massive infarction was common in the shock group, an equal number of patients who were not graded as shocked were found to have extensive infarction. Conversely not all patients with cardiogenic shock had extensive infarction.

Estimations about the size of the infarcted area are

difficult to interpret. Unequivocal gross changes do not become apparent for some 24 to 48 hours following occlusion of a major coronary artery in man, although minimal microscopic evidence of infarction amy be recognised as early as 6 hours in man (Mallory, White and Salcedo-Salgar, 1939). Nachlas and Shnitka (1963) developed a technique for macroscopic identification of infarction based on alterations of dehydrogenase activity in the myocardium. Their technique involved staining the myocardium with Nitro-BT /- 2, 2′ di-nitrophenyl, 5, 5′, diphenyl 3, 3′ (3, 3′ dimethoxy 4, 4′ biphenylene) ditetrazolium chloride -/. This substance utilises a general dehydrogenase reaction. In the viable muscle where endogenous substances, co-enzymes and dehydrogenases are present, reduction of Nitro-BT yields a dark blue formazan; necrotic muscle fibres remain unstained. Bouch and Montgomery (1970) utilised this technique to examine 100 consecutive autopsies from the Coronary Care Unit of the Royal Infirmary, Edinburgh. Their findings showed that when sensitive techniques were used the infarcted area was always large in cardiogenic shock. The pathological findings do not yet allow interpretation of the precise sequence of events; early shock might occur with a small infarct, and prolonged hypotension and inadequate coronary perfusion might lead to more extensive infarction. Further developments in pathological and clinical techniques are required to determine the sequence of events following infarction.

If there is not a significant hypovolaemia in cardiogenic shock the finding of a low stroke volume would argue that there is severe impairment of the left ventricle. Ross (1967) suggested another possibility that asynergy or asynchrony of the left ventricle may be a major feature of cardiogenic shock. This argument was used by Nixon, Ikram and Morton (1966), when they first reported their successful use of volume expansion. In 2 of their patients there was a high central venous pressure and further elevation was brought about by the infusion of 5% laevulose, and at the same time there was an improvement in both patients' clinical condition. They suggested that after infarction an increased left ventricular volume decreased cardiac asynergy and improved left ventricular function.

In this thesis only changes that may occur in the circulation when the patient is in sinus rhythm have been considered. This has been done because although the clinical features of cardiogenic shock may occur in patients with arrhythmias, correction of the arrhythmias usually reverses the shock syndrome. However, not all patients will be improved. We have reported (Lassers, Anderton, George, Muir and Julian, 1968) a study of the haemodynamic effects of pacing in complete heart block complicating acute myocardial infarction. Whilst pacing increased cardiac output in most patients, stroke volume fell as the heart rate increased, indicating myocardial performance was

abnormal. In 3 patients there was no increase in cardiac output with artificial pacing. These 3 patients all exhibited the features of cardiogenic shock both before and after pacing. Future studies on shock complicating myocardial infarction could include patients with heart block provided it had been demonstrated that there was no improvement after an adequate trial of pacing. Similarly, patients who have had other arrhythmias and have been returned to sinus rhythm but still continue to demonstrate the clinical features of shock could also be included.

In summary although most careful circulatory studies have shown left ventricular failure in cardiogenic shock, there exists a number of reports casting doubts on these findings. Cardiogenic shock may not be a unitary concept and there may be differing circulatory states masquerading under one clinical guise. One of the main difficulties in interpreting many of the studies in acute myocardial infarction is the difficulty in clinical definition. That clinical classification alone is inadequate, is demonstrated by the wide disparity in reported cardio-respiratory findings in patients who are severely ill following acute myocardial infarction. It is important to try to find an objective definition or definitions to categorise the patients and allow an adequate evaluation of various therapeutic regimes. Moreover it is only by an understanding of the abnormal physiology in the severe grades of myocardial infarction that a logical therapeutic schedule can be devised.

METHODS

CHAPTER II

METHODS

One of the major advances in the management of the severely ill patient is the introduction of various bedside monitoring techniques. The value of E.C.G. monitoring for the detection and treatment of arrhythmias has been demonstrated (Lawrie et al. 1967). In the investigation and treatment of patients who have hypotension and low cardiac outputs, facilities which allow measurement of pressure and flow are of great value. In 1965 MacKenzie described the provision of a specially equipped room attached to a general medical ward so that such measurements could be made.

Many of the studies described in this thesis were conducted in this intensive care room, but continuing work in the management of acute myocardial infarction and in other areas of intensive care, have revealed the need for more mobile equipment. The equipment can then be taken to the patient rather than the patient moved to the special investigational area.

During these studies the equipment has undergone considerable modification but the essential features have been:

1. Pressure recording facilities with transducers, amplifiers and portable recording facilities.
2. Cuvette densitometer assembly with output to the

recorder for the measurement of cardiac output.

3. Facilities for rapid injection of dye and constant withdrawal pump.

4. Electro-cardiogram with output to recorder and separate output to oscilloscope to provide continuous patient monitoring.

This equipment can now be mounted on one single trolley and can be taken to the bedside of a patient who is seriously ill. This allows better patient monitoring and the circulatory observations provide information for a more rational therapeutic policy in the management of the individual patient.

PRESSURE RECORDING

1. Catheter Technique:

Systemic Arterial Pressure was obtained using a small bore nylon catheter (Portex O.D. 1.34 mm. length 30 cm). This was introduced percutaneously into the brachial artery using a modified Seldinger technique. In 2 patients with cardiogenic shock the brachial artery was not palpable, and the femoral artery was catheterised.

Right Atrial or Central Venous Pressure was obtained by advancing a no. 7 double lumen Cournand catheter from an antecubital vein. The position of the catheters was judged to be adequate, when there was a good respiratory movement on the pressure recording.

Right Ventricular and Pulmonary Arterial Pressure was obtained

by various modifications of the technique described by Bradley (1964). In this technique a small polyethylene catheter is allowed to 'float' into the pulmonary artery. The position is judged by the pressure wave form obtained. The technique demands a compromise between small catheters which enter the pulmonary artery easily and larger versions which allow adequate pressure recordings and blood sampling. Most of the studies were performed with a Portex O.D. 0.75 mm. catheter but the Phillips pulmonary catheter 6.113.09 has proved even easier to use in more recent studies, providing a better pressure wave form and allowing easier sampling of mixed venous blood.

2. Recording System:

Zero reference point was 5 cm. below the sternal angle.

All pressures were transduced using a Statham P23 Db strain gauge manometer. Appropriate calibration values were obtained from an open saline column, aneroid manometers or mercury column manometers.

The pressures were recorded on a Honeywell U.V. recorder* or in special circumstances a Rikadenki 3 pen recorder+.

3. Frequency Response:

The measurement of systolic and diastolic pressure peaks

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*Honeywell Controls

+Rikadenki Kogyo

requires a catheter system of relatively low frequency response (6 cycles/second). To record mean pressures the recording system can have a very low frequency response. However, the frequency response of micro catheter systems is not known and to determine the dynamic frequency response of our own system a series of studies were carried out.

The method was a modification of the technique described by Fry (1960). A hole was bored in the barrel of a 20 ml. syringe, by blocking the hole with a damp finger and pressing the plunger, a pressure is generated. If the finger is quickly released the drop in pressure produces a square wave. A square wave transmitted through the complete recording system (i.e. catheter, transducer, amplifier and recorder) allows a check on the dynamic frequency response.

The square wave is recorded with an overshoot. The overshoot is used to obtain a damping ratio h

$$h = \sqrt{\frac{\left(\ln \frac{x_2}{x_1}\right)^2}{\pi^2 + \left(\ln \frac{x_2}{x_1}\right)^2}}$$

Where the quantity $\ln \frac{x_2}{x_1}$ is the natural logarithm ratio of the amplitudes of any two successive excursions in the oscillatory transient response to the stepwise change in pressure.

Knowing h, the undamped natural frequency ω_u can be computed

$$\omega_u = \omega_d / \sqrt{1-h^2} \quad \text{radians/sec. or cycles/sec.}$$

ω_d is the damped natural frequency, this is calculated from the frequency of after vibrations of the transient response to the square wave. The dynamic frequency of whole system i.e. the Portex O.D. 0.75 mm. catheter, Statham transducer amplifier and U.V. recording system was 15.49 ± 4.32 cycles/sec. Where the Rikadenki pen recorder was used the system was limited by the frequency response of the pen recorder which was 6 cycles/sec. Small air bubbles caused marked damping and the frequency response of these micro catheters was markedly improved by a period of continuous flushing.

CARDIAC OUTPUT DETERMINIATIONS

In the present studies cardiac output was determined by the dye dilution technique using indocyanine green as an indicator. This method was first described by Stewart in 1897.

The introduction of better indicators and accurate quick reading densitometers has allowed development of the original technique. Details of the method used in the Department of Medicine, the University of Edinburgh, have been described by MacKenzie (1965) and Sapru (1966). The essential features and later modifications in technique are outlined below.

General Principles: A small accurately known amount of indicator

is injected into the right side of the circulation. Its subsequent dilution is proportional to the flow of blood. By sampling blood from the left side of the circulation and recording the dilution curve produced, an estimate of the cardiac output can be made.

Dye Injection: Approximately 2 ml of indocyanine green was injected rapidly by allowing compressed air to drive close the plunger of a specially made syringe. This was automatically reloaded after each injection from a reservoir. The activation of the syringe controlled a 3 way tap to allow injection to the patient and re-filling from the reservoir.

The syringe was made so that a fixed volume was delivered at each injection. At the end of each study, the actual injected volume was determined by weighing 4 flasks before and after a bolus injection. The injected volume varied from study to study but in any one patient never varied by more than 0.01 ml.

Dye Dilution Sampling: Immediately before the injection of the dye, arterial blood was withdrawn from the arterial line through a cuvette and this sampling continued until the dye dilution curve had been completed. A constant withdrawal rate was maintained throughout the sampling period by using the Harvard constant infusion-withdrawal pump (Harvard Apparatus Co. Inc.) and using 50 ml Luer-Lock syringes. The cuvette densitometer was the Waters x 300 system. This consists of a cuvette with two cadmium selenium photocells, one with maximum sensitivity at 800 Å, the wave length of indocyanine green dye, while the other cell gave minimal transmission at this wave length.

The passage of dye through the cuvette creates an imbalance in the cuvette which is part of a Wheatstone bridge. The resultant signal is amplified and the output can be described on any suitable recorder.

Measurement of Dye Curves: In an ideal system there is no recirculation and a bolus injection produces a curve which rises rapidly to a peak and then decays in exponential fashion. Cardiac output is inversely proportional to the area under the curve. In man recirculation occurs so that only the early part of the decay curve is exponential. Recirculation can be accounted for if the exponential part of the decay is extrapolated to zero and the area under this curve measured (Hamilton, Moore, Kinsman and Spurling, 1932, Zierler, 1962).

Method of Calibration: Calibration involved a whole blood technique. 40 ml of blood was removed from the patient at the end of the study. This was placed on a siliconised flask containing a small amount of heparin (0.5 ml of 25,000 units.ml heparin with chlorocresol preservative). After thorough mixing the actual calibration was carried out.

Using a micro-pipette (Micro-Repette, Gencons) a small volume of dye was injected into a 10 ml flask. This micro syringe is capable of delivering 10 micro litres to an accuracy of $\pm$ 1.5%. Double and treble the dye volume was injected into two further 10 ml flasks. These flasks were then made up to 10 ml from the stored blood. The flasks were sealed and inverted repeatedly to

ensure adequate mixing. The remaining 10 ml of blood was used for base line control.

The calibration blood was withdrawn through the cuvette at the same withdrawal rate as that used in the study in ascending order of concentration. The average value of the three steps was taken as the calibration factor. In other words 10 μ litres of dye diluted in 10 ml of blood produced a calibration step of x cms.

These factors were then used in the equation:

$$\text{Cardiac output l/min} = \frac{60 \times I}{\sum c \times F}$$

Where I is dye injectate volume

$\sum c$ is sum of heights of dye curve at second intervals measured in centimetres.

F is calibration factor in ml.cm.

BLOOD GAS TENSIONS AND pH.

These were measured on an Instrumentation Laboratories Inc. type 113-SI ultra-micro pH and blood gas system. The accuracy of this instrument in our laboratory has been described (Flenley, Millar and Rees, 1967).

Oxygen tensions were measured using a Clark polarographic electrode. A polarising voltage is applied which reduces oxygen diffusing through a gas-permeable membrane. This reduction produces a flow of electrons and it is this current which is

measured. The electrode was calibrated using "white spot" nitrogen as zero reference and humidified air as the high reference point. Where the high scale was used, humidified oxygen was used as the high reference point.

Carbon dioxide tensions were measured using a Severinghaus type electrode which measures change in pH in a electrolyte solution due to diffusion of CO_2 through a gas-permeable membrane. This electrode was calibrated using CO_2 mixtures of approximately 3 and 10%. The precise levels were determined by Lloyd Haldane analysis of the gas mixtures.

pH was measured using a glass electrode and calomel reference electrode. The electrode was calibrated using precision buffers of 6.81 and 7.383 (Radiometer Copenhagen).

All readings were made at 37°C. With this system duplicate analysis can be performed on sample volumes of 2 ml.

OXYGEN SATURATION AND OXYGEN CARRYING CAPACITY

Oxygen Saturation: Oxygen saturation was measured directly and also derived from the oxygen tension. The direct method was the haemo-reflector method described by Zijlstra (1957). Although this technique is widely used there are a number of disadvantages. As oxygen saturations falls the haemoreflector method becomes less accurate (Cole and Hawkins, 1967). Variations in haemoglobin concentration will also introduce errors as the technique depends on

light reflection (Zijlstra 1957). The sample volume required is approximately 5 ml. Using the 'float-in' catheter to enter pulmonary artery samples as large as this are difficult to obtain. Thus arterial oxygen saturation was measured directly whilst venous oxygen saturation was derived from measured oxygen tension and pH using the data of Severinghaus (1966). This method is open to criticism as well. The conversion to oxygen saturation is made on the steep portion of the haemoglobin dissociation curve and small errors in measurement of oxygen tension could be magnified on conversion to saturation; thus a 1 mm error in oxygen tension will lead to a 3% error in venous oxygen saturation. Moreover, it is possible that all patients do not have the same haemoglobin dissociation curves (Metcalfe, Dhindsa, Edwards and Mourdjinis (1969). Despite these technical considerations, the measurement of oxygen tension and conversion to saturation is adequate for clinical purposes. Ideally total oxygen content should be measured but the sample volume required for the standard method is large and difficult to obtain through a float catheter. Micro-method for the measurement of total oxygen content are available and are likely to be improved (Linden, Ledsome and Norman, 1965).

Oxygen Carrying Capacity: This was measured by light transmission using a spectrophotometer (Unicam Instruments Ltd. SP600). This method was standarised against the Van Slyke manometric method (Staunton, 1966).

MEASUREMENTS AND CALCULATIONS

Pressure and Flow:

Intravascular pressures and heart rate were measured as the average of 15 second values falling about the definitive point. Mean pressures were obtained by electronic damping. Cardiac output determinations, measured by the techniques described earlier, were made at 5 minute intervals. Results were corrected for body surface area. In the presentation of haemodynamic variables in chapter III the values given are the average of at least 4 determinations.

Systemic vascular resistance was calculated according to the formula.

$$\text{Systemic Vascular Resistance } (\text{dynes.sec.cm}^{-5}\text{m}^{2}) = \frac{\text{Mean Aortic Pressure}}{\text{Cardiac Index}} \times 1332 \times 60$$

Stroke volume was obtained by dividing the cardiac index by the heart rate.

Gas Exchange:

Temperature correction and derivation of oxygen saturations were made on the calculator described by Severinghaus (1966).

As estimate of alveolar oxygen tension (PAO_2) was made using the formula derived from Riley, Cournand and Donald (1951).

$$PAO_2 = PIO_2 - \frac{PaCO_2}{R} \quad (I\text{-}FIO_2 \; /\bar{I}\text{-}R\_/)$$

where PIO_2 is the inspired oxygen tension.

FIO_2 is the fraction of oxygen in the inspired gas.

$PaCO_2$ is the arterial carbon dioxide tension.

Gas collections were not made routinely; the respiratory exchange rate was assumed to be 0.80. The derived alveolar oxygen tension was used to calculate the oxygen content of end-pulmonary capillary blood. The difference between alveolar and arterial oxygen tensions is expressed as the alveolar to arterial difference ($A\text{-}aDO_2$). The main components of this difference or gradient result from

(a) a component of venous admixture due to scatter of ventilation: perfusion ratios in different parts of the lung.

(b) shunted unoxygenated venous blood which mingles with oxygenated blood leaving the pulmonary capillaries.

The contribution made by ventilation: perfusion ratios may be estimated using the equation

$$\frac{Qva}{Qt} = \frac{C\acute{c}O_2 - CaO_2}{C\acute{c}O_2 - C\bar{v}O_2}$$

where Qva is the venous admixture.

Qt is the total blood flow.

$C\acute{c}O_2$ is the oxygen content of end-pulmonary capillary blood.

CaO_2 is the oxygen content of arterial blood.

$C\bar{v}O_2$ is the oxygen content of mixed venous blood.

After the patient has inspired a high level of oxygen for 20 to 30 minutes, it is assumed that all alveoli are fully oxygenated and that blood leaving these alveoli should be fully saturated. Any arterial hypoxia then occurring can be attributed to perfusion of non-functioning gas exchanging units. This has been called the "true shunt" and is calculated as

$$\frac{Qs}{Qt} = \frac{C\acute{c}O_2 - CaO_2}{C\acute{c}O_2 - CvO_2}$$

where Qs is the "true shunt"

This equation assumes that all shunted blood is mixed venous and no allowance is made for shunting occurring in the Thebesian and bronchial veins.

In the calculation of oxygen content at high levels of inspired oxygen it is important to include the amount of dissolved oxygen in the plasma.

PATIENT SELECTION

Individual details of patients are documented in relevant sections. Myocardial infarction was diagnosed using the criteria of the World Health Organisation (1959). They suggested that patients could be classified as

A "Very probable" myocardial infarction if they satisfied the following criteria:

a) Association of Q,I not less than 20% of R,I and negative T,I (a sign of anterolateral infarction has to be confirmed by precordial leads).

b) Association of Q,II and negative T,II, Q,II and negative T,III and QVF. Q at least 25% of the largest R wave in III and not less than 0.03 sec. in II and III.

c) Q waves in precordial leads V_1, V_2, V_3 and negative or diphasic T waves in V_2 and V_3 (QRS not exceeding 0.10 sec.). When no R wave present = QS configuration).

d) Q waves more than 0.4 mV in precordial leads V_4 and V_5 or 0.2 mV in V_6 in association with negative T waves in these leads.

e) Injury current - evolution and disappearance in three stages.

B "Possible" myocardial infarction:

With changes in ST segment T wave changes suggestive of infarction accompanied by a rise in serum enzymes.

Of the 70 patients studied and presented in this thesis, 59 fulfilled the criteria for diagnosis as "very probable myocardial infarction". 11 were "possible" myocardial infarctions. In these patients, serum enzymes were elevated, the serum creatinine kinase > 80 i.u. or serum aspartate aminotransferase (SGOT) > 50 Reitman and Frankel units.

An approximate estimate of the severity of the infarct was

made by classifying the patients as (1) uncomplicated, (2) with left ventricular failure, (3) with cardiogenic shock. The uncomplicated cases were those who exhibited no evidence of shock or left ventricular failure. Left ventricular failure was judged to be present when there was widespread lung crepitations and dyspnoea, in the absence of a history of bronchitis. Cardiogenic shock was diagnosed when there was pallor, cold skin, restlessness and oliguria with a systolic blood pressure remaining below 100 mm Hg measured by sphygmomanometry. In addition these patients were without marked dyspnoea. All the patients were in normal rhythm and there was no improvement in the shock state half an hour after the relief of pain and administration of oxygen. This classification is similar to that used by Freis et al. (1952) and MacKenzie (1965).

CARDIO-RESPIRATORY STUDIES IN ACUTE MYOCARDIAL INFARCTION

CHAPTER III

CARDIO-RESPIRATORY STUDIES IN ACUTE MYOCARDIAL INFARCTION

RESULTS:

A Clinical Status

The patients were grouped into 3 broad clinical groups defined in Chapter II. The clinical features of each patient was recorded prior to investigation. There were 26 patients with uncomplicated myocardial infarction and a summary of the clinical features in these patients is shown in Table 3. These patients were studied during investigations into the action of opiates in acute myocardial infarction. For this reason it was important that no patient had received drug therapy within 12 hours of the investigations, thus some of the patients were not studied immediately after admission, but all patients were studied within 36 hours of infarction. In the groups with left ventricular failure or shock, such a drug free period could not be obtained and these patients were investigated shortly after admission to hospital. No patients had pressor therapy prior to the investigation. There were 10 patients in the group with left ventricular failure (Table 4). In the group with shock there were 7 patients (Table 5). One of these patients,TA, survived the shock state, but on the following day developed severe

left ventricular failure. This patient was studied twice and the clinical features whilst shocked and whilst in left ventricular failure are shown in the appropriate tables.

Chest x-rays were interpreted according to the criteria of Steiner (1969). They were defined as abnormal if they showed:

1. Pulmonary venous distension or congestion in the upper zones indicating reversal of blood flow and differential vasoconstriction.
2. Pulmonary oedema: no distinction was made between intra-alveolar pulmonary oedema (batswing) and interstitial pulmonary oedema (septal lines).

A summary of the autopsy findings is shown in Table 6. In 4 of the 7 autopsies there was evidence of old ischaemic damage to the ventricle. In all but one autopsy the recent damage, as demonstrated by the Nitro BT stain, was very extensive. In patient TA who had survived the shock state and developed left ventricular failure and had died later from a cerebral embolism, there was only a small area of ischaemic damage on the anterior border of the left heart.

B Cardio-Respiratory Status

The observations in patients with uncomplicated myocardial infarction and left ventricular failure were made whilst breathing room air. In the group with shock, only initial blood gas tensions were obtained whilst the patients were breathing air, all other observations were made whilst the patients were breathing high flow

oxygen through a polymask (B.O.C.). Our own observations suggests that with this mask and oxygen flow rates over 10 litres min, the patient is breathing approximately 65% oxygen.

Cardio-respiratory measurements of the uncomplicated group (group I) are given in Table 7, of the group with left ventricular failure (group II) in Table 8 and of those with shock (group III) in Table 9. Where the data is presented in diagramatic form, the data of MacKenzie (1965) is also shown.

Arterial Pressure: The systolic arterial pressure in patients with uncomplicated myocardial infarction ranged from 101 to 233 mm Hg (mean 136 S.E.M. $\pm$ 6.54 mm Hg) whilst in those patients with left ventricular failure from 80 to 156 mm Hg (mean 116 $\pm$ 8.57 mm Hg). In the patients with shock, systolic arterial pressure ranged from 52 to 112 mm Hg (mean 71 $\pm$ 7.96 mm Hg) (fig. 1). When the groups are compared using a non-paired 't' test the t value for group I compared with group II is $1.69 > 0.05$. However, systolic blood pressure was significantly lower in the group with cardiogenic shock (t 3.67, $0.001 < p < 0.005$).

In 3 of the 'shocked' patients, blood pressure could not be obtained by conventional sphygmomanometry whilst in the other patients with shock cuff blood pressure readings bore little relation to intra-arterial pressure. Patient A1 had a systolic blood pressure of 75 mm Hg by sphygmomanometry but the recorded intra-arterial systolic pressure was 112 mm Hg.

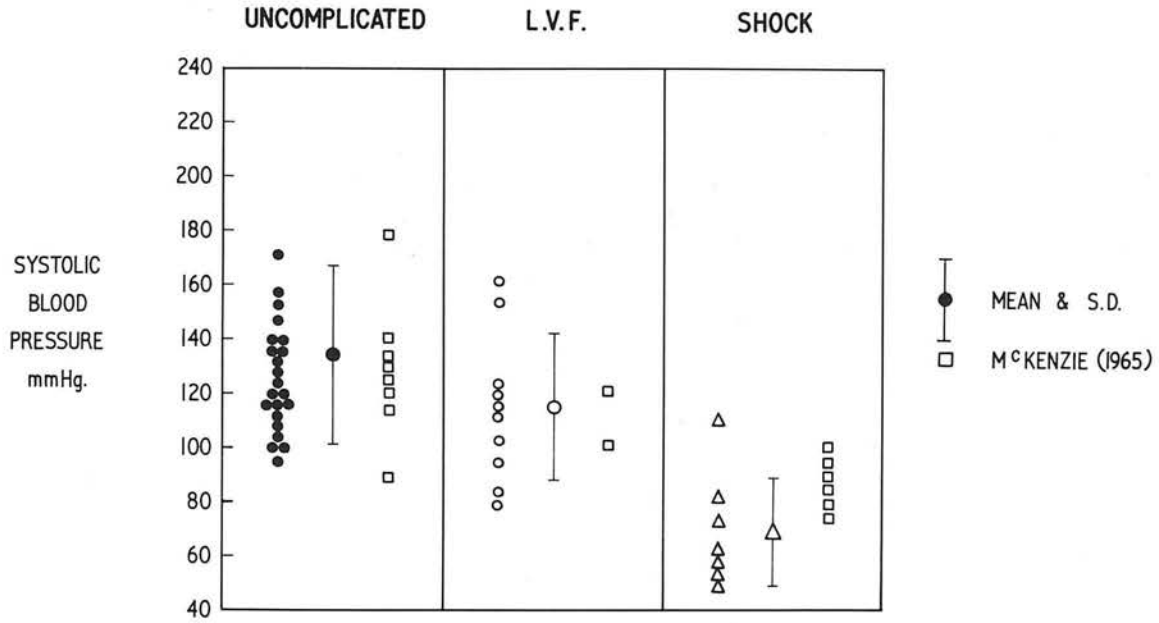


Fig. 1

Systolic arterial blood pressure in acute myocardial infarction. The standard deviation is drawn on the data presented in this chapter. In addition the individual values obtained by MacKenzie (1965) are plotted (□) but are not included in the calculation of the standard deviation.

Mean arterial pressure (fig. 2) for group I ranged from 56 to 164 mm Hg (mean 101 ± 4,48 mm Hg); in group II the range was from 60 to 125 mm Hg (mean 83 ± 7.17 mm Hg); in group III mean arterial pressure ranged from 40 to 94 mm Hg (mean 56 ± 7.08 mm Hg). The more severely ill patients had the greater reduction in mean arterial pressure (I:II t 2.11, $0.025 < 0.05$; II:III 2.68, $0.01 < p < 0.02$).

There was a less marked difference in diastolic blood pressure in the more severely ill. The mean diastolic pressure was 78 ± 3.69 mm Hg in group I, in group II 66 ± 5.86 mm Hg and in group III 47 ± 6.78 mm Hg. Because of the wide range of recordings the differences between groups I:II and II:III were not statistically significant, although group III was significantly lower than group I (t 4.62, $p < 0.001$).

Cardiac Output: The mean output corrected for body surface area was 2.71 ± 0.075 litres.min.m^2 in the uncomplicated group. Cardiac index ranged from 1.96 to 3.39 litres.min.m^2. The cardiac index in the group with left ventricular failure was significantly lower (mean 2.09 ± 0.154 litres.min.m^2) (t 4.05, $p < 0.001$). The cardiac index in the shocked group was significantly lower (mean 1.34 ± 0.055 litres.min.m^2) than the group with left ventricular failure; (t 3.94, $0.01 < p$ 0.02). Despite the highly significant difference between the 3 groups there was an overlap in cardiac output determinations, the patients with left ventricular failure

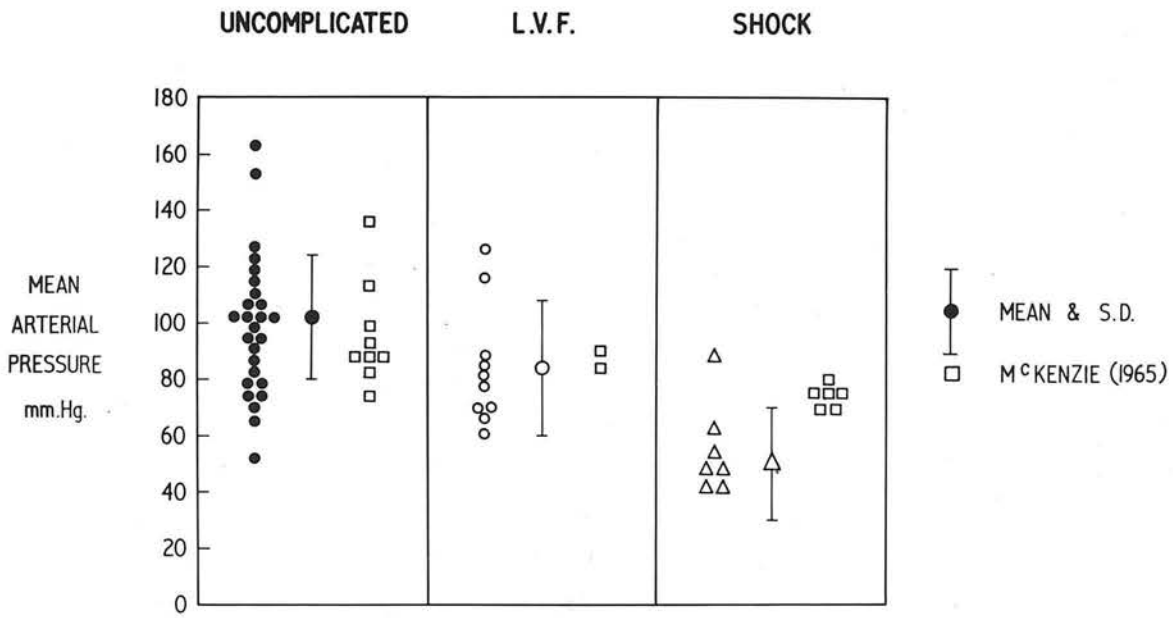


Fig. 2

Mean arterial blood pressure in acute myocardial infarction. Presentation details are the same as in Fig. 1.

having a wide range of values (1.29 - 2.79 litres.min.m^2) (fig. 3). There was no such overlap between groups I and III.

Heart Rate: (fig. 4) There was a wide range of heart rates for all groups and although heart rates were usually higher in the groups with failure and shock there was no significant difference between the groups (I:II t 1.87, $p > 0.05$, II:III t 0.60, $p > 0.05$).

Stroke Volume: (fig. 5) The mean stroke volume (stroke index) for group I was 33 $\pm$ 1.47 ml.m^2. This was significantly higher than in the group with left ventricular failure (mean 23 $\pm$ 2.70 ml.m^2) (t 3.34, $0.001 < p < 0.005$). In group III there was a marked reduction in the stroke volume with a mean value of 13.5 $\pm$ 1.13 ml.m^2 (group II:III t 2.84 $0.01 < p < 0.02$). Again there was considerable overlap so that some of the patients with left ventricular failure had stroke volumes as high as in the uncomplicated group, whilst others had markedly reduced stroke volumes and as low as some of the patients with cardiogenic shock (fig. 6).

Systemic Vascular Resistance: The relationship of calculated systemic vascular resistance to systemic arterial pressure, cardiac output and the gradings of infarction is shown in fig. 7. There was no significant difference between the groups (I:II t 0.80, $p > 0.05$; II:III t 0.30, $p > 0.05$). It is of note that only one patient with cardiogenic shock had a calculated systemic vascular resistance outside normal limits (A1, 6730 dynes sec $cm^{-5} m^2$).

Right Atrial Pressure: (fig. 8) The mean right atrial pressure for

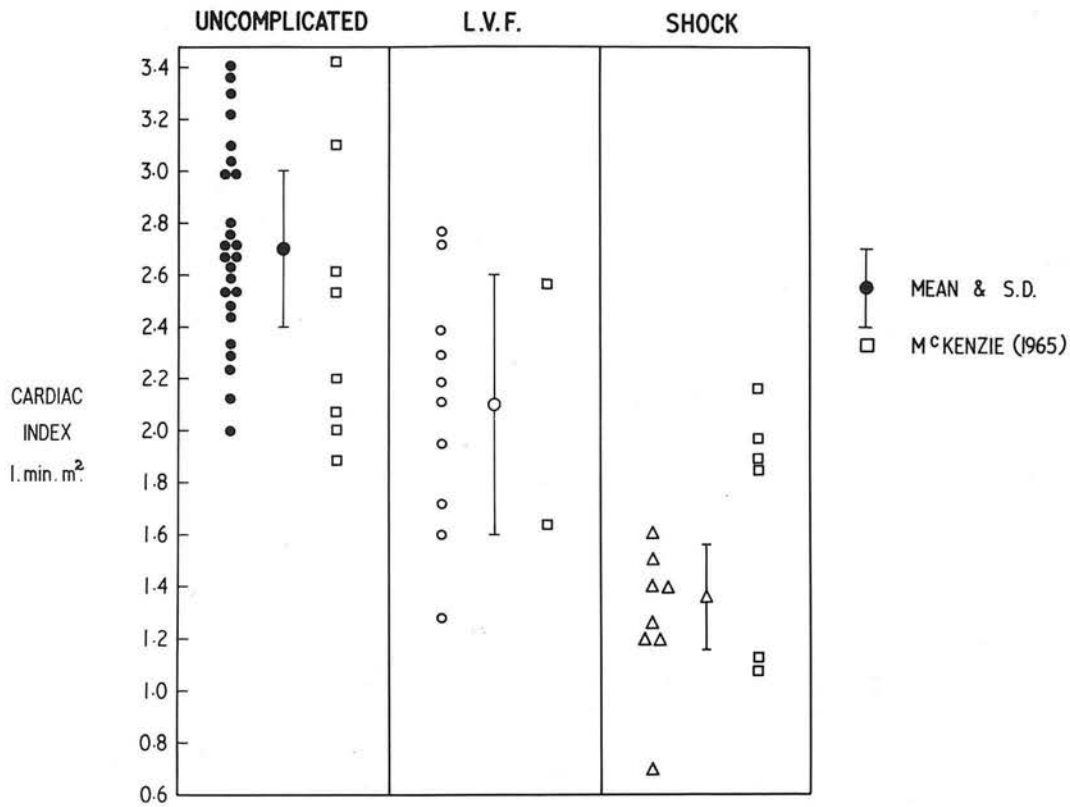


Fig. 3

Cardiac output, corrected for body surface area, in acute myocardial infarction.

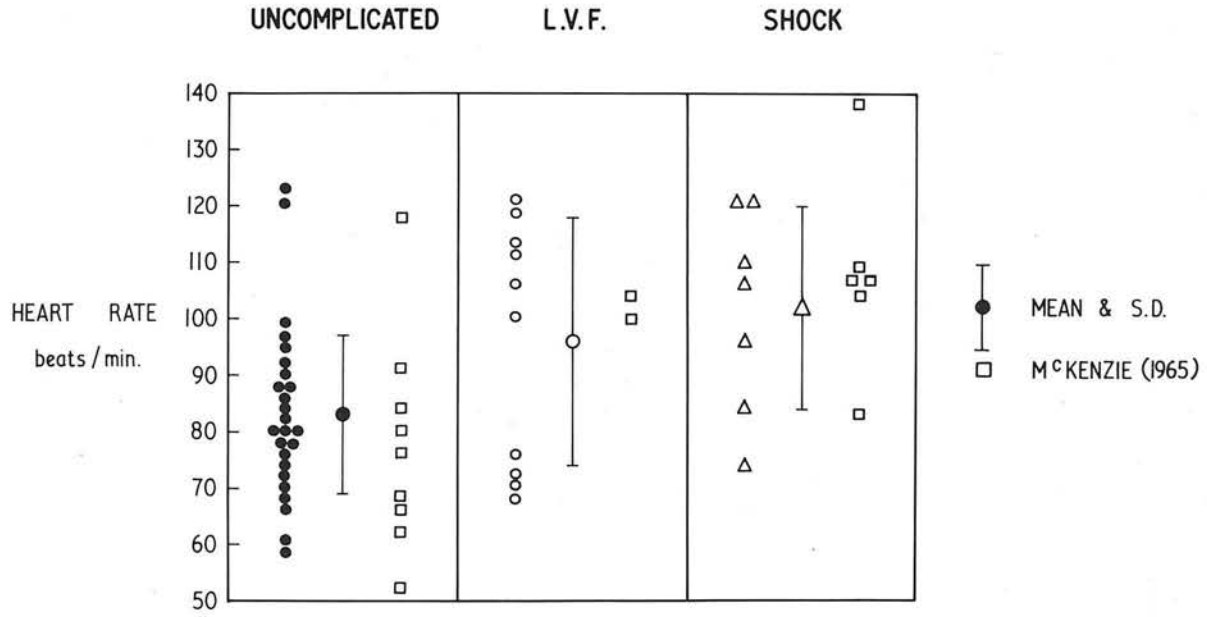


Fig. 4

Heart rate in acute myocardial infarction.

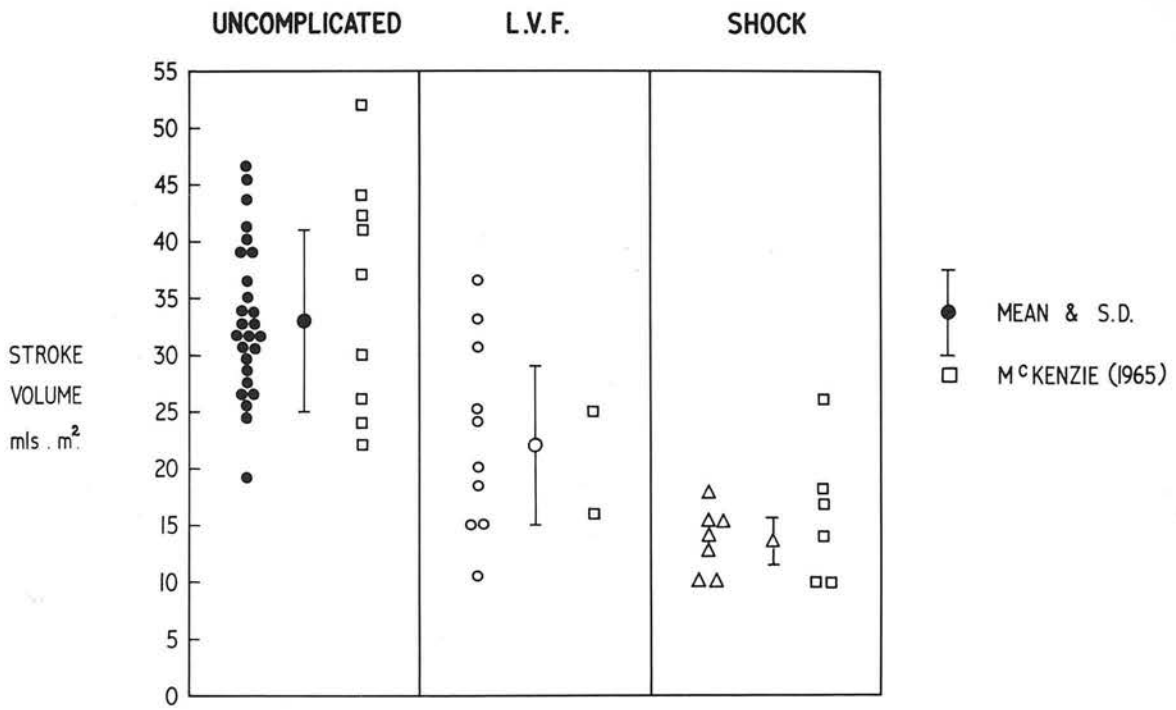


Fig. 5

Stroke volume, corrected for body surface area, in acute myocardial infarction.

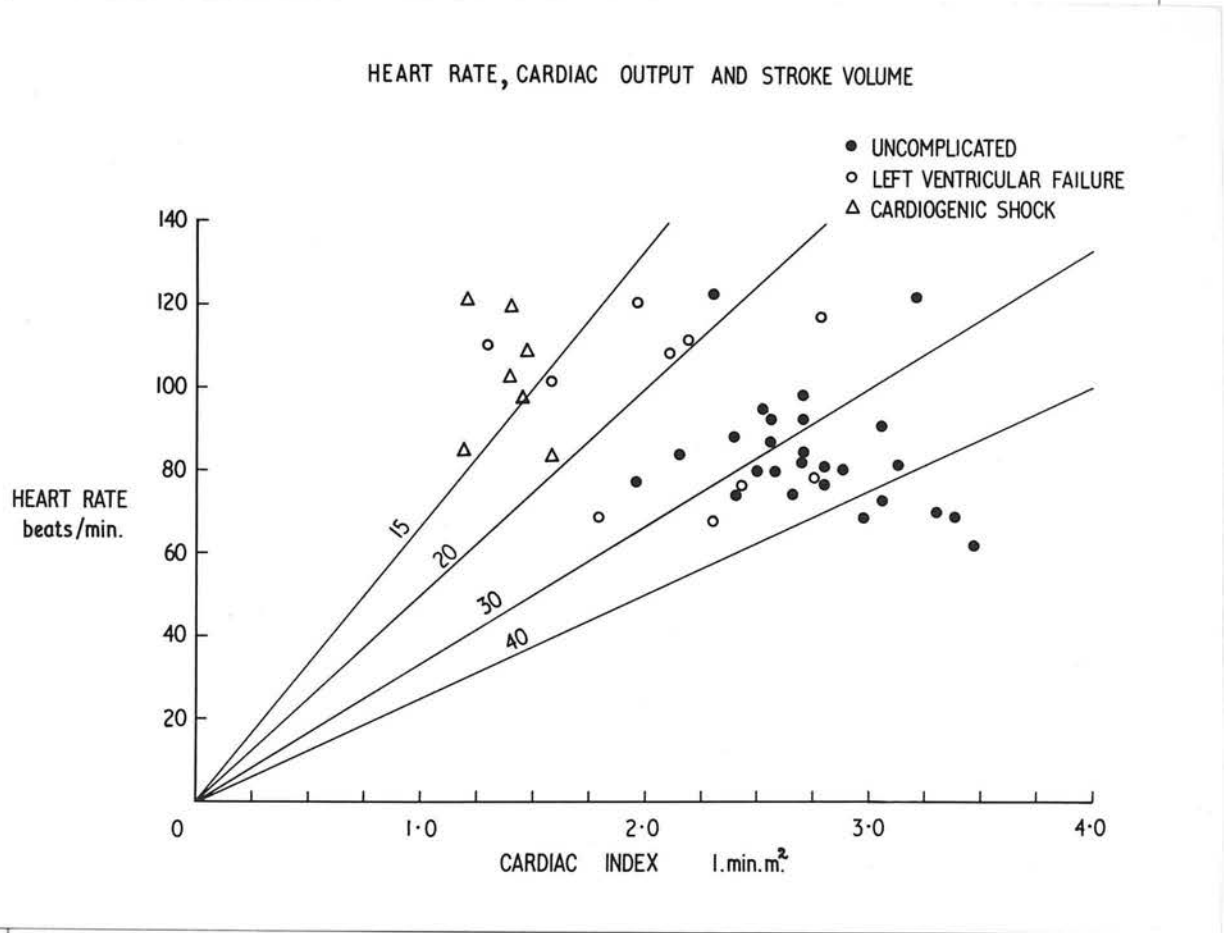


Fig. 6

The relationship of cardiac output to heart rate in varying degrees of severity of acute myocardial infarction. Isopleths represent the calculated stroke volume in mls m^2.

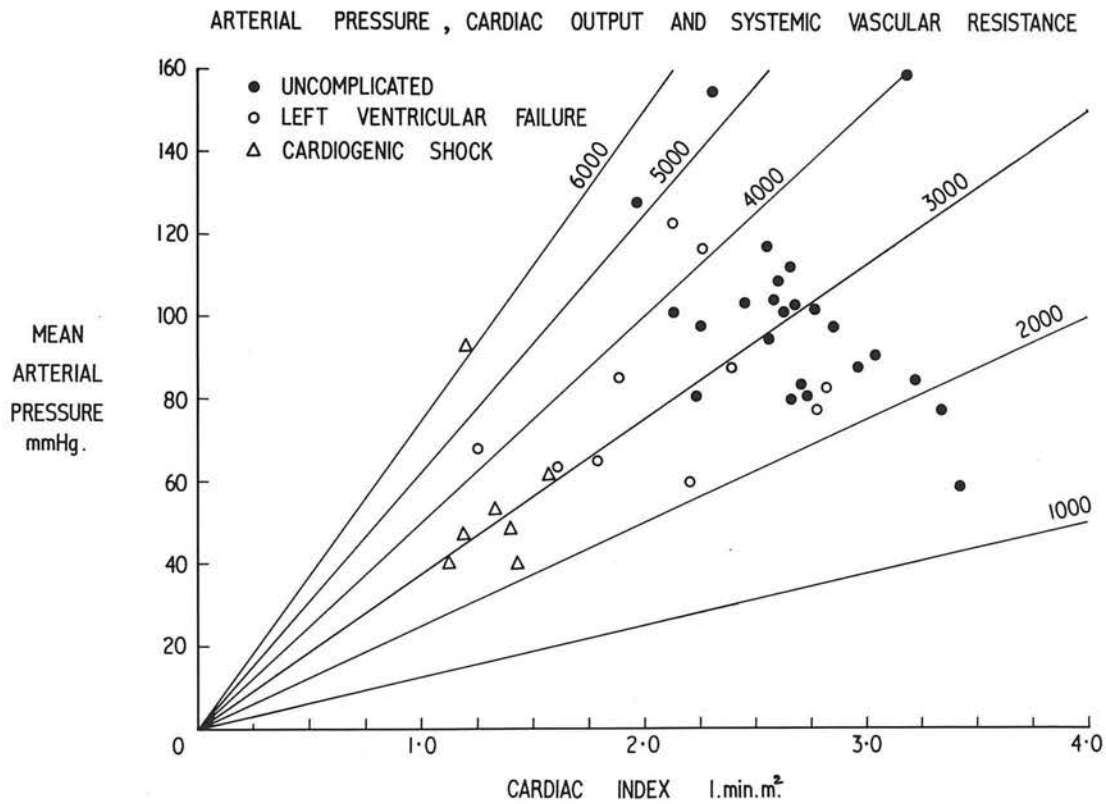


Fig. 7

The relationship of cardiac output to mean aortic pressure in varying degrees of severity of acute myocardial infarction. Isopleths represent the calculated systemic vascular resistance in dynes sec $cm^{-5}m^{2}$.

group I was 3.8 ± 0.59 mm Hg. 4 patients in this group had right atrial pressures greater than 5 mm Hg. In the group with left ventricular failure, the lowest right atrial pressure was 4 mm Hg and the mean for the group was 8.3 ± 1.04 mm Hg. This was significantly greater than the mean pressure for group I (t 3.95, $p < 0.001$) but there was no significant difference between group II and group III (t 0.101, $p > 0.05$).

Pulmonary Arterial Pressure: (fig. 9) In 3 patients these observations were made using a Cournand No. 7 catheter and in these patients the pulmonary artery wedge pressure is also recorded in Table 8. In 33 patients pulmonary artery pressure was measured using the flow guided catheter described in chapter II. In 7 patients no measurement could be made for technical reasons, usually due to failure to pass the small catheter up a peripheral vein. These findings occurred in the earlier studies and newer catheters and more experience made the passing of this catheter a relatively simple technique. There was no serious arrhythmia caused by the introduction of this catheter into the pulmonary artery.

The mean pulmonary arterial pressure in group I was 19 ± 1.56 mm Hg. In one patient (MU) the pulmonary artery pressure was markedly elevated at 40 mm Hg. On subsequent review, the chest x-ray of this patient showed pulmonary venous congestion. The mean pulmonary arterial pressure was significantly greater in group II

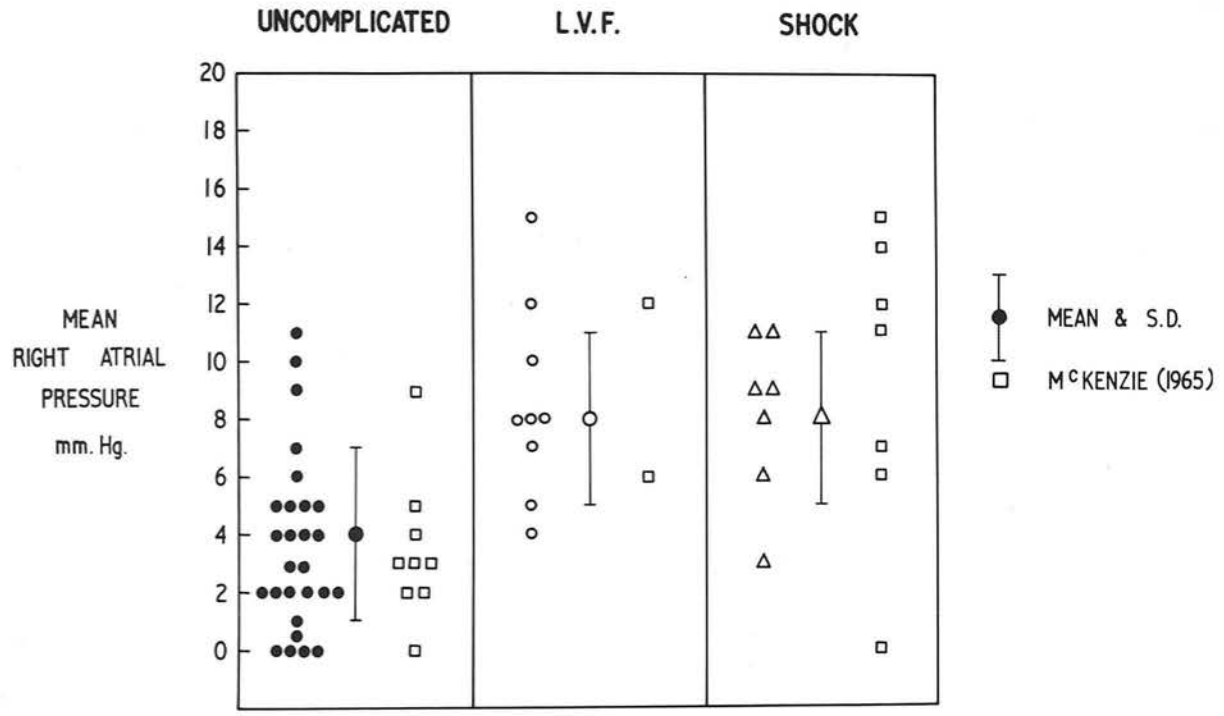


Fig. 8

Mean right atrial pressure in acute myocardial infarction.
In the report by MacKenzie zero reference point was at the sternal angle. For comparison purposes his right atrial pressures have been corrected to a zero reference point 5 cms below the sternal angle.

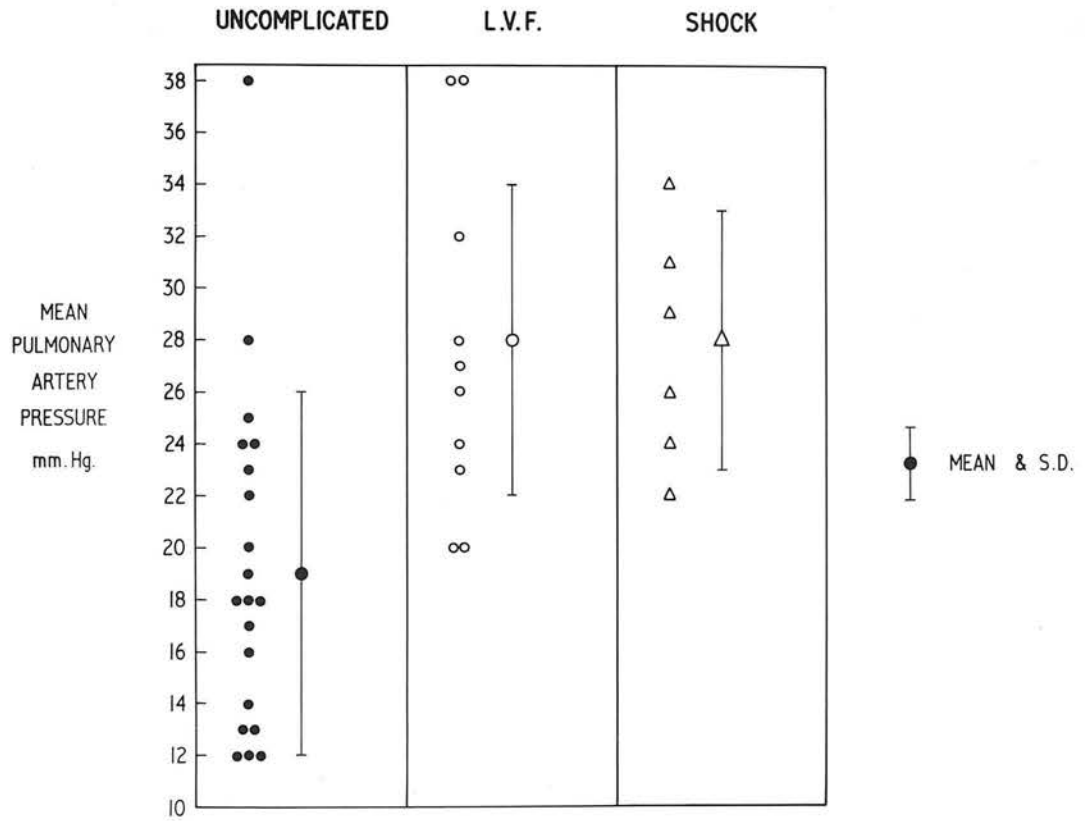


Fig. 9

Mean pulmonary arterial pressure in acute myocardial infarction. (Pulmonary artery pressure was not measured by MacKenzie).

than group I (mean 27.6 ± 2.08 mmHg) (I:II t 3.15, $0.001 < p < 0.005$). The mean pulmonary arterial pressure in cardiogenic shock was also elevated (mean 28 ± 1.84 mm Hg), but this was not significantly different from the group with left ventricular failure (t 0.02, $p > 0.05$). The relationship of right atrial pressure to pulmonary arterial pressure is shown in fig. 10.

Arterial Oxygen Tension: (fig. 11) The PaO_2 was reduced in all groups with the lowest values being found in patients in groups II and III. The range of PaO_2 for patients with uncomplicated myocardial infarction was from 42 to 80 mm Hg (mean 64 ± 2.11 mm Hg). There was no significant difference between mean PaO_2 in group II (54 ± 3.52 mm Hg) and group III (mean 54 ± 6.46 mm Hg) whilst breathing air, but whilst breathing > 60% oxygen the patients in group II had an increase in PaO_2 similar to group I, whilst those in group III had only a small rise in PaO_2 (fig. 12). There was one exception, patient TA, in group II. This patient had severe and intractable pulmonary oedema and intermittent positive pressure ventilation was instituted. Despite hand ventilation via an endotracheal tube with 100% oxygen, the PaO_2 was only increased to 88 mm Hg. In a similar situation in a patient not reported in this series, but with cardiogenic shock, intermittent positive pressure ventilation with 100% oxygen produced an arterial oxygen tension of 320 mmHg.

Carbon Dioxide Tensions: (fig. 11) It is usually held that carbon

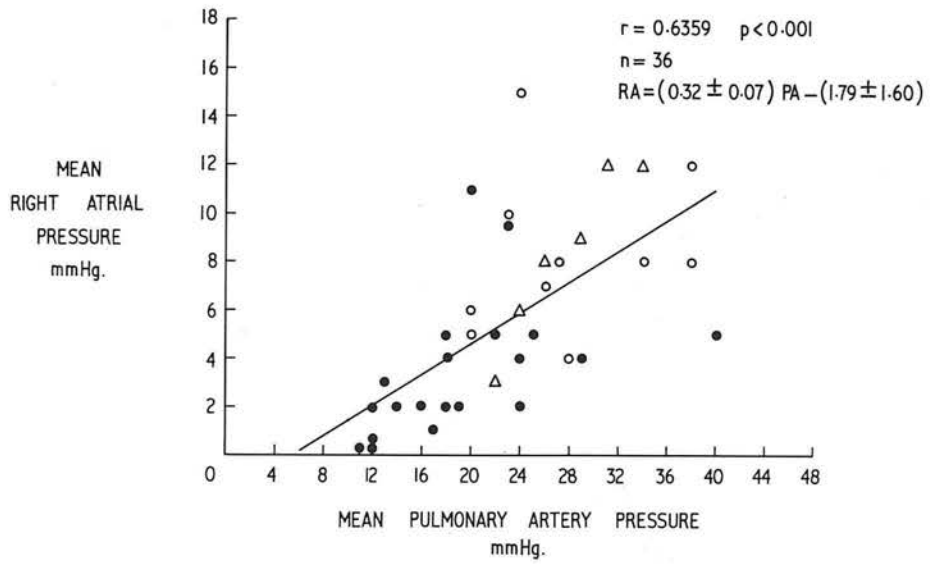


Fig. 10

The relationship of right atrial pressure to pulmonary arterial pressure in acute myocardial infarction. (Regression line calculated by the least squares method).

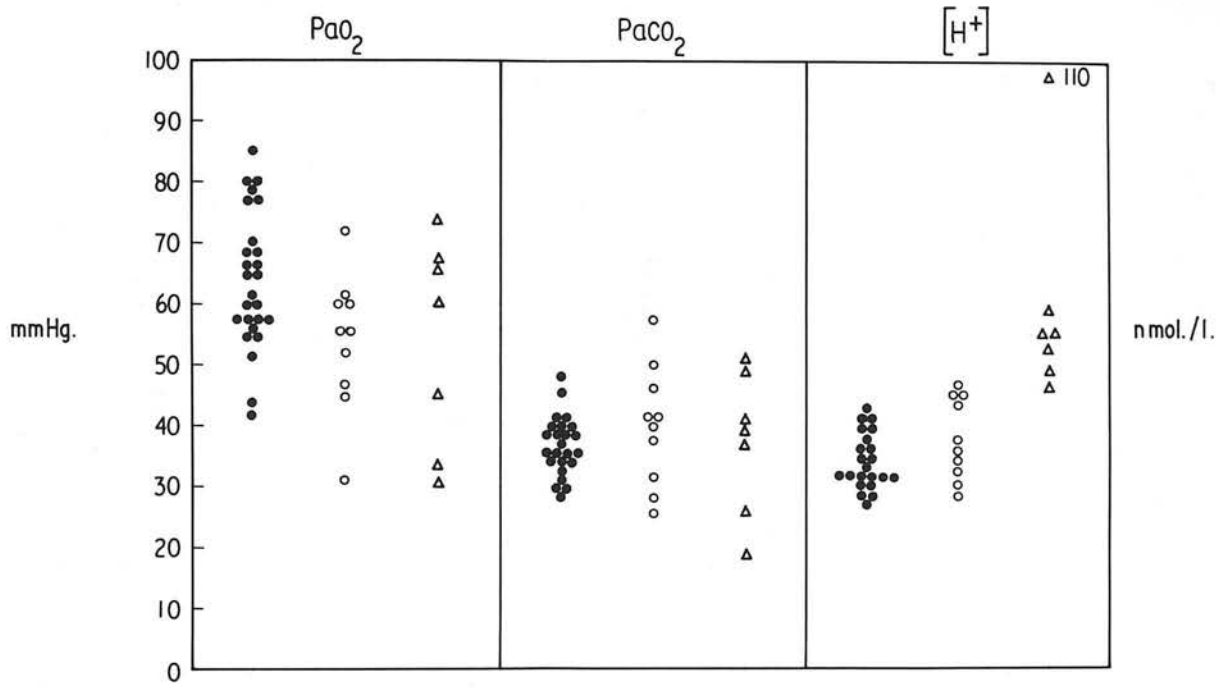


Fig. 11

Arterial oxygen tension, carbon dioxide tension and hydrogen ion concentration in acute myocardial infarction.

Group symbols are the same as in previous diagrams.

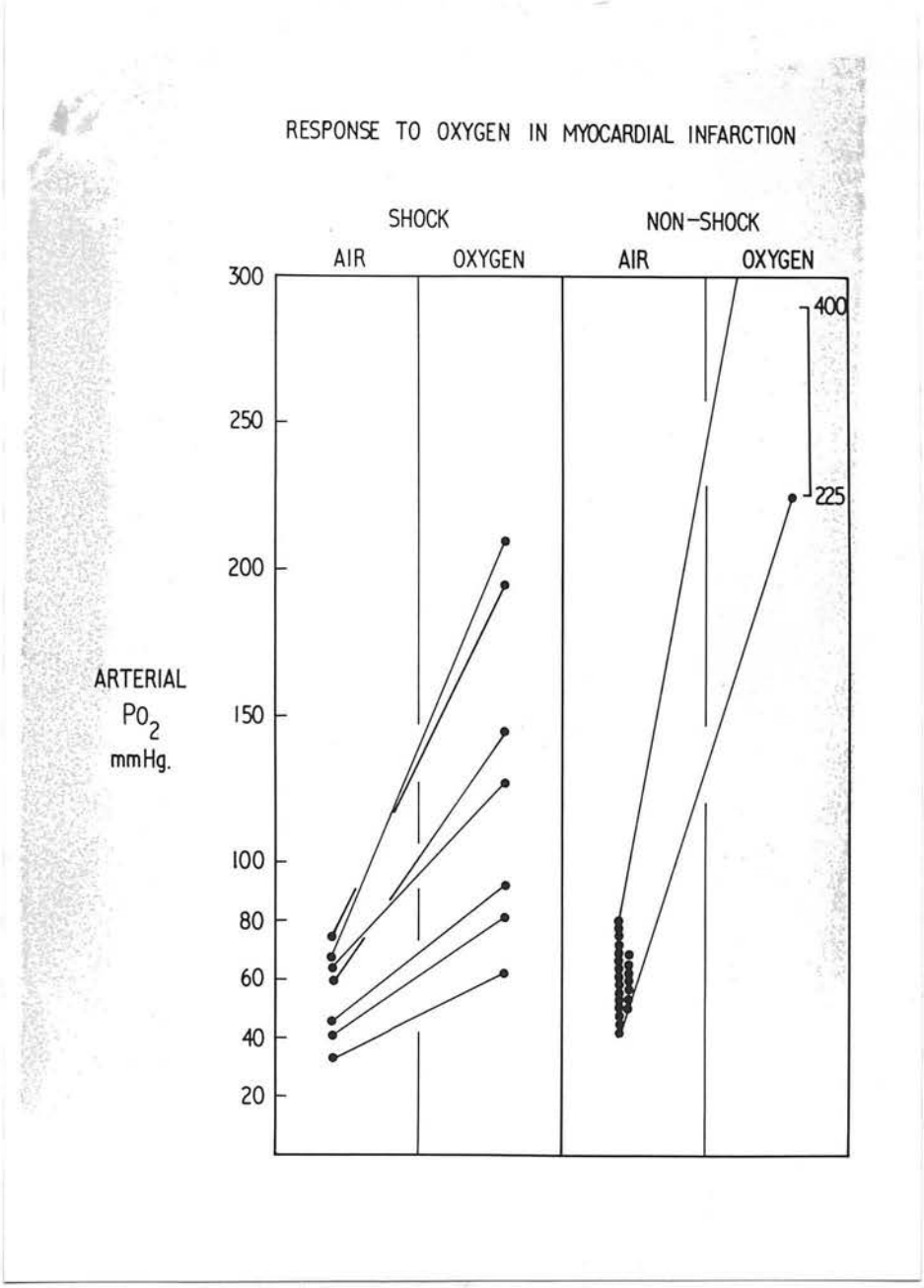


Fig. 12

Response to oxygen therapy (approximately 65% O_2) in acute myocardial infarction. The non-shock group consists of patients from groups I and II.

dioxide tensions are reduced in left ventricular failure. Although several patients with left ventricular failure had a very low $PaCO_2$ the mean $PaCO_2$ was not significantly different from the other 2 groups. One of the patients with a high $PaCO_2$ in group II had chronic bronchitis and in this patient (FI) a small dose of pethidine brought about an even greater increase in carbon dioxide tension. The patient made a satisfactory recovery from his infarct but his $PaCO_2$ remained elevated after discharge from hospital.

Arterial pH: The pH values for each group are shown in Tables 7, 8 and 9 and these values have been converted into hydrogen ion concentrations for graphical display in fig. 11. The pH was low in all patients with cardiogenic shock. In 3 of the patients with left ventricular failure, the pH was below 7.40. As a simple attempt to describe the acid-base status of the patients the standard bicarbonate of each group was calculated. In group I the mean standard bicarbonate was 27.0 $\pm$ 0.71 mequiv. litre, in group II, 25.1 $\pm$ 1.48 mequiv. litre and in group III 16.6 $\pm$ 1.78 mequiv. (I:II t 1.32, $p > 0.05$) (II:III t 3.67, $0.001 < p < 0.005$).

Mixed Venous Oxygen Saturation ($\bar{S}v\bar{O}_2$): (fig. 13) For technical reasons this was only obtained in 30 patients. The patients with uncomplicated myocardial infarction had a mean $\bar{S}v\bar{O}_2$ of 63.6 $\pm$ 1.70%. In the patients with left ventricular failure $\bar{S}v\bar{O}_2$ was significantly lower at 46.0 $\pm$ 3.74 (t 5.287, $p < 0.001$). The patients with cardiogenic shock are not strictly comparable as they were all

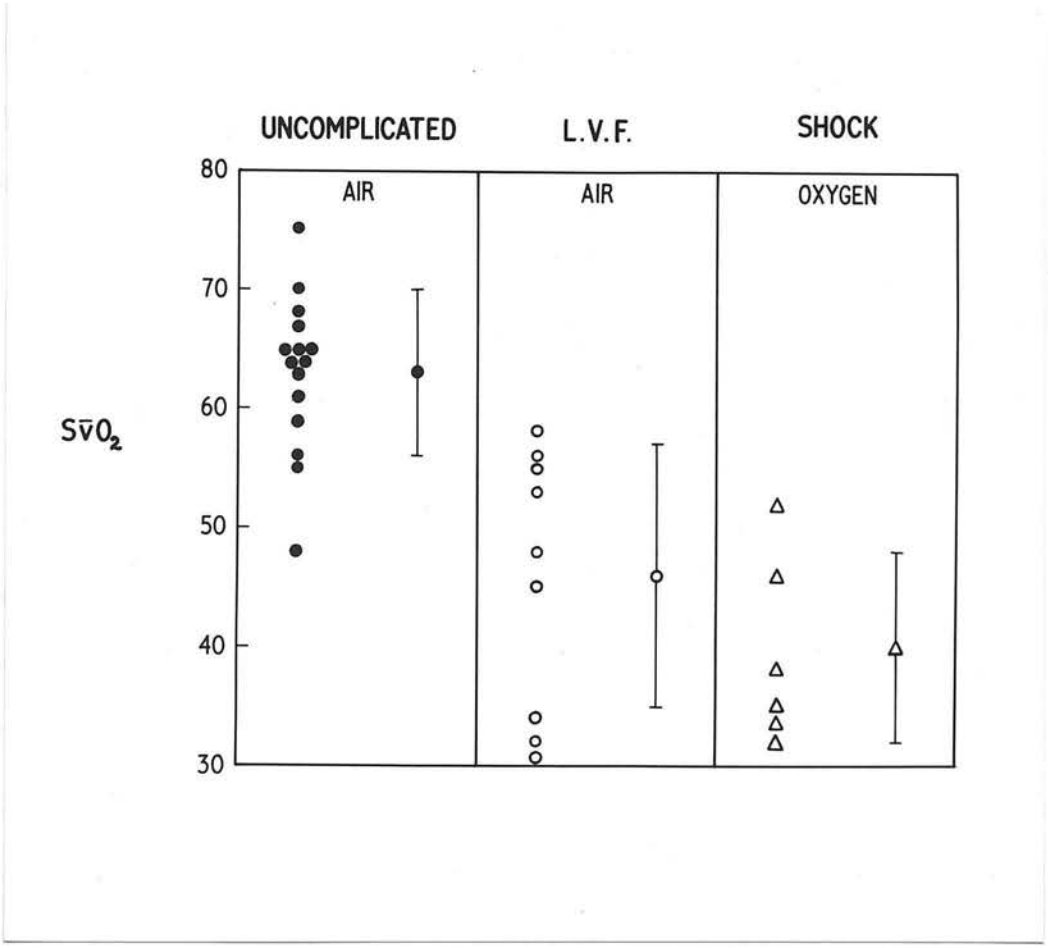


Fig. 13

Mixed venous oxygen saturations in acute myocardial infarction. Patients with shock were breathing oxygen whilst this measurement was made.

breathing > 60% oxygen whilst $S\bar{v}O_2$ was measured. In this group the mean $S\bar{v}O_2$ was 40.0 ± 3.20%. The relationship of cardiac index to $S\bar{v}O_2$ is shown in fig. 14.

Arterio-Venous Oxygen Difference: The measured arterio-venous oxygen difference in group I ranged from 2.19 to 9.18 vols.% (mean 6.22 ± 0.467 vols.%). In group II the range was from 4.98 to 12.6 vols.% (mean 7.87 ± 0.796 vols.%) (t 1.92, $p > 0.05$). Again group III were not strictly comparable as they were breathing high concentrations of oxygen. In this group the mean arterio-venous difference was 9.84 ± 1.447 vols.%).

The patient in group I with the high pulmonary arterial pressure (MU) had a low mixed venous oxygen saturation (48%) and the highest arterio-venous oxygen difference measured in group I (9.18 vols.%).

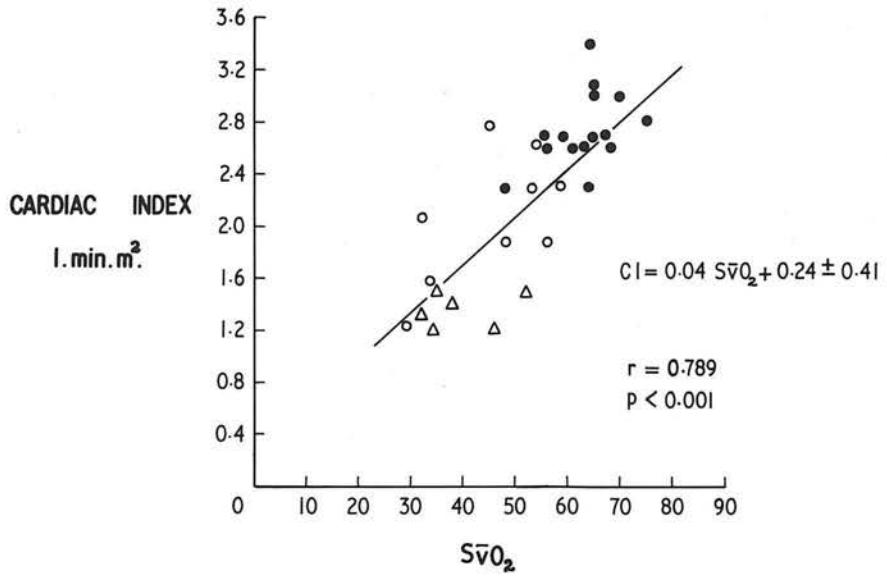


Fig. 14

The relationship of mixed venous oxygen saturation to cardiac output in varying degrees of clinical severity of acute myocardial infarction. Each clinical group is represented by the same symbol as in the previous diagram.

DISCUSSION

Arterial pressure is a relatively poor guide to the severity of infarction for, although systolic arterial pressure was reduced in patients with cardiogenic shock, systolic arterial pressure was also low in some patients with uncomplicated myocardial infarction and left ventricular failure. A low level of blood pressure has often been used as an index of the patients' clinical condition and as a guide to the necessity for therapeutic support. Thomas, Malmcrona and Shillingford (1965) reported on the haemodynamic features of 7 patients with hypotension after myocardial infarction. Their paper can be criticised on methodological grounds; dye dilution curves were determined using a photoelectric ear-piece, despite the presence of clinical shock in some of their patients; not all of the investigations were performed during the acute stage. However, they did demonstrate that cardiac output could be normal or low in patients with hypotension. From their data it appeared that low blood pressure per se was relatively unimportant in determining the clinical course of the patient. However, the measurement of intra-arterial pressure is of real value in cardiogenic shock because of discrepancies between cuff blood pressure and intra-arterial pressure in shock. Intra-arterial pressures provided the only accurate means of determining blood pressure in shock and of following responses to therapy. In addition mean or diastolic pressure recordings are more likely to be of value in low output

states as these levels are more important determinants of coronary blood flow than is systolic pressure. If some measurement of blood flow can also be made then much more precise information about the patient's circulatory condition can be given.

The detailed observations of MacKenzie (1965) had shown considerable reduction in cardiac output in those patients with cardiogenic shock. There was some reduction in cardiac output in patients with uncomplicated myocardial infarction so that to a certain extent the two groups overlapped. The stroke volume determinations for the two groups showed little overlap and he suggested that some of the shocked patients managed to maintain an adequate cardiac output by an increase in heart rate. He also noted that patients with shock had a high right atrial pressure and a normal or raised central blood volume. The low stroke volume without signs of hypovolaemia suggested severe impairment of left ventricular function in cardiogenic shock. In his study he had made observations on only two patients with left ventricular failure but the findings in those patients were of reduced cardiac output and stroke volume to almost the same extent as in the patients with cardiogenic shock.

Normal values for cardiac output at rest have been compiled by Wade and Bishop (1962). They suggested that values above 4.6 litres min m^2 and below 2.4 litres min m^2 were unlikely to be found in normal subjects. On this basis, 5 of the patients in the uncomplicated group in the current study had a low cardiac output.

Furthermore the majority of the remainder had a cardiac output in the low normal range. 8 of the 10 patients with left ventricular failure and all the patients with cardiogenic shock had a low cardiac output. Indeed in this study there was no overlap between the shocked patients and those with uncomplicated myocardial infarction and there was a progressive reduction in cardiac output with the increasing clinical severity. There was also a similar reduction in stroke volume with the increasing clinical severity of the infarction. Some of the difficulties inherent in the measurement of cardiac output in low output states were mentioned in Chapter I. The very slow circulation makes the inscription of the dye curve lengthy. Recirculation of dye from such areas as coronary circulation may occur relatively early in the dye curve so that determinations of the area under the curve are inaccurate. A further source of error may be introduced by the correction for body surface area; a more accurate standardisation could be achieved by correction for lean body mass. Despite these considerations, cardiac output determinations presented in this chapter show a consistent trend and are in close agreement with the studies of MacKenzie (1965). Minor differences in results can be attributed as much to the relative inaccuracy of the methods as to biological variation.

Systemic vascular resistance did not differ significantly between the 3 groups of patients. The systemic vascular resistance is the resultant of the vascular resistances of all vascular beds

in the systemic circulation and cannot be equated with regional vasomotor tone. Nevertheless the concept of total systemic vascular resistance can be useful. If systemic resistance were consistently increased, the shock state might be viewed as a net vaso-constriction, conversely if resistance were consistently decreased a net vaso-dilatation would exist. In this series as in the reports of MacKenzie (1965) Shubin et al. (1968), Gunner et al. (1966) in the shocked patients systemic vascular resistance showed no consistent trend. MacKenzie (1965) had demonstrated that vaso-constriction in these patients was by no means maximal as patients could produce a marked increase in systemic vascular resistance during the act of vomiting. He suggested that the characteristic abnormality was a failure to elevate resistance rather than the presence of an excessive resistance. Smith et al. (1967) suggested that hypoxia and acidosis might diminish the normal vaso-constrictor response. Indeed if shocked patients are given vaso-pressor therapy, there is an increase in mean arterial pressure (MacKenzie 1965, Smith et al. 1967), but at the expense of a decrease in cardiac output. At present it would seem wise to interpret changes in total systemic vascular resistance with caution. More attention should be directed at regional perfusion and blood flow for the changes in regional blood flow in low output states are probably of more importance in determining the precise metabolic responses in acute myocardial infarction and in the development of shock complicating infarction.

The elevated right atrial pressures found in patients with left ventricular failure and shock support the concept of increasing left ventricular dysfunction with increasing clinical severity. This finding is similar to that of MacKenzie (1965) but the measurement of pulmonary arterial pressures extends the studies by MacKenzie. Pulmonary arterial pressure was raised in 8 of the 26 patients with uncomplicated myocardial infarction. Radiological changes suggestive of left sided failure were noted in 7 of the patients with so-called 'uncomplicated' myocardial infarction and 5 of these were patients with raised pulmonary arterial pressures. Lassers, George, Anderton, Higgins and Philp (1970) in a study of patients with atrio-ventricular and bundle branch block complicating acute myocardial infarction had also noted that radiological changes were in general associated with increased pulmonary arterial pressures, but in a number of patients there were radiological changes of left heart failure without elevation of pulmonary arterial pressures. Radiological changes of pulmonary oedema may persist after transient elevation of left heart pressures.

In all the patients with left ventricular failure and with cardiogenic shock, pulmonary arterial pressures were raised. It might even be considered somewhat surprising that pulmonary arterial pressures were so high in the group with shock in view of the marked reduction of cardiac output and systemic pressure in this group.

Recently Field and Cotes (1970) studied the relationship of pulmonary artery pressure to cardiac output in patients with chronic bronchitis. The pulmonary arterial mean pressure was similar in patients with and without breathlessness, but the relation of pulmonary artery pressure to cardiac output was higher in the group with breathlessness. Breathing oxygen during exercise led to a reduction in pulmonary arterial pressure in all subjects, but not to a change in the slope of the mean pressure flow curve. Although they were using their data as evidence of a vascular sluice effect in the pulmonary circulation, their report is a useful reminder of the importance of considering pressure in relation to flow. Thus the pulmonary arterial pressures recorded in cardiogenic shock are indeed high in relation to the low cardiac outputs demonstrated in this condition.

The relationship of pulmonary artery pressures to left ventricular pressures has been questioned and is the subject of a number of studies. Sapru (1966) found a close correlation between pulmonary arterial wedge pressure and left ventricular end-diastolic pressure in patients with left ventricular failure, although such a close relationship was not found by Linden and Allison (1963). Kaltman, Herbert, Conroy and Kossman (1966) were able to show that in the absence of mitral valve obstruction, diastolic pulmonary arterial pressures closely correlated with left ventricular end-diastolic pressures in patients with congenital and acquired heart

disease. Lassers et al. (1970) found a good correlation between diastolic pulmonary arterial pressure and pulmonary arterial wedge pressure in patients with acute myocardial infarction. There was also a good correlation between mean pulmonary arterial pressure and pulmonary arterial wedge pressure. In this study because of poor frequency response of the earlier micro-catheter systems, only mean pulmonary arterial pressure was recorded. With better catheter systems and adequate frequency response in the portable recording system, pulmonary artery diastolic pressures would be easily obtained.

Although left ventricular pressures were not measured in the patients in this study, the high mean pulmonary arterial pressures demonstrated in the patients with shock or failure, suggest that both groups had severe impairment of left ventricular function. There was no evidence of a low filling pressure in any of the shocked patients and there was no evidence of hypovolaemia. The consistent pattern demonstrated in this study suggests that patients with cardiogenic shock represent the most severe reaction to left ventricular infarction with haemodynamic evidence of left ventricular failure.

However, it must be considered that not all patients with cardiogenic shock have the same haemodynamic pattern. It is possible that patients who had had diuretic therapy before infarction, who are seen many hours after infarction, or have been

treated with vaso-pressors after infarction, might present with cardiogenic shock due to volume depletion. None of the patients in this series were treated with vaso-pressors and all were studied shortly after admission. Detailed examination of the case reports by Nixon's group (Nixon et al. 1966, 1967 and 1968a, b, a) suggest that all of the cases they studied were somewhat abnormal in that shock developed after prolonged treatment, in association with arrhythmias or after surgery. Until there is more evidence on this point, it would seem wise that all patients with cardiogenic shock should have some monitor of left heart pressures. For the present pulmonary arterial pressures are probably adequate but in the future direct readings of left ventricular pressures are more likely to be widely used. The relationship between right atrial pressure and mean pulmonary arterial pressure shown in fig. 10 is too wide to allow indirect estimation of pulmonary arterial pressures in individual patients.

The present studies confirm the high incidence of arterial hypoxaemia in acute myocardial infarction demonstrated by MacKenzie et al. (1964), McNicol et al. (1965) and Valentine et al. (1966); although hypoxaemia was marked in patients who were critically ill, the arterial oxygen tension was equally low in patients with left ventricular failure and cardiogenic shock. By use of data obtained whilst the patients were breathing air, the majority of patients could be demonstrated to have an increase in venous admixture (group I 16 $\pm$ 2.2%; group II 22 $\pm$ 5.3%; group III 36 $\pm$ 8.3%).

Formal studies with high levels of oxygen were only carried out in the patients with cardiogenic shock and in one patient with left ventricular failure. If the venous admixture was due to veno-arterial shunting then there would be little change in the degree of admixture after breathing high levels of oxygen. Fig. 15 shows venous admixture whilst breathing air (Qva) and oxygen (Qs) and one can conclude that the arterial hypoxia in cardiogenic shock is due to abnormalities both in ventilation perfusion ratio and in veno-arterial shunting. In the patients with uncomplicated acute myocardial infarction, arterial oxygen tensions whilst breathing approximately 65% oxygen ranged from 225 to 400 mm Hg. Approximate estimates of the veno-arterial shunt (Qs) at this high level of oxygen in the inspired gas suggest that the true shunt in this group is low (< 10%) and that the major cause of arterial hypoxia in this group is due to abnormal ventilation-perfusion ratios.

This data is similar to that of McNicol et al. (1965) and Pain, Stannard and Sloman (1967) but is in contrast to the results of Valentine et al. (1966). Valentine and colleagues had suggested that ventilation perfusion imbalance was the major cause of hypoxaemia in acute myocardial infarction. Pain, Stannard and Sloman (1967) had found abnormal veno-arterial shunting together with defects in the matching of pulmonary ventilation to pulmonary blood flow. They did not relate their findings to clinical severity but the present data suggests that in most patients after myocardial infarction

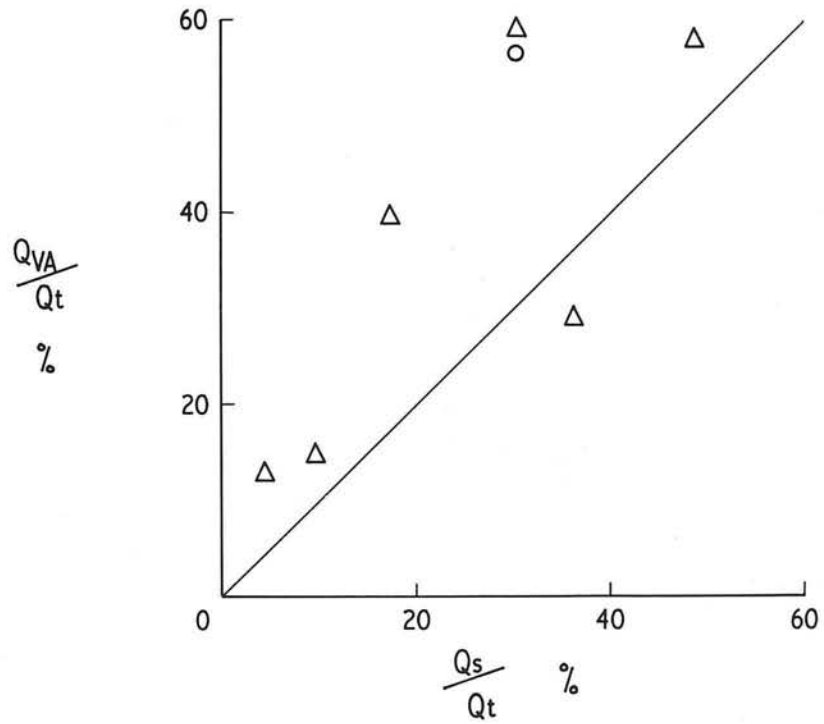


Fig. 15

The relationship of venous admixture (Qva) to "true" shunt (Qs) in 6 patients with shock and one patient with left ventricular failure complicating acute myocardial infarction. If hypoxaemia were due to veno-arterial shunting alone, then the points would lie along the line of identity.

there is an abnormal ventilation perfusion pattern and in those who are seriously ill there is in addition an increase in veno-arterial shunting.

By use of a radioactive xenon technique, Kazemi, Parsons, Valenca and Streider (1970) have shown that after acute myocardial infarction there is a marked reduction in perfusion to the lung base and increased perfusion to the apex. The pattern of perfusion abnormality is probably a reflection of the increase in pulmonary venous pressures.

Disturbances of ventilation might be caused by narrowing of airways owing to intrabronchial or peribronchial oedema due to congestion of lung vessels associated with a rise in left atrial pressure. The failure to obtain normal oxygen tensions in the more severely ill patients after oxygen therapy suggests non-functioning gas exchanging units. These may be filled with alveolar exudate, or collapsed due to marked peribronchial cuffing or to loss of alveolar surfactant. In cardiogenic shock abnormalities of gas transfer may be increased by the low flow through the lung but the similarity of findings in shock and left ventricular failure suggests that the major defect is associated with pulmonary oedema.

The increase in carbon dioxide tension in pulmonary oedema was first noted by Anthonisen and Smith (1965). In a 6 month period, 4 patients were admitted to the Royal Victoria Hospital, Montreal, with a marked respiratory acidosis complicating acute pulmonary oedema.

Avery, Samet and Sackner (1970) made a study of 109 patients with pulmonary oedema. They excluded patients with cardiogenic shock, cardiac arrest, chronic bronchitis, chronic uraemia or diabetic ketoacidosis. Fifty-five of their patients had a combined metabolic and respiratory acidosis. In the present study one patient with left ventricular failure had chronic bronchitis and his $PaCO_2$ remained elevated after recovery from infarction, but in the other patients with left ventricular failure and a raised $PaCO_2$ there was no evidence of co-existing disease. The administration of opiates does produce an increase in carbon dioxide tensions (Chapter VI), but usually only 5 mm Hg. Carbon dioxide retention in the patients with severe left ventricular failure is probably due to inability to maintain an adequate minute ventilation because of extensive airway collapse and obstruction by oedema fluid and foam. Higgs (1968) has shown a large increase in dead space tidal volume (Vd/Vt) ratio in patients with pulmonary congestion following acute myocardial infarction. With an increased physiological dead space, an apparently adequate minute ventilation may be insufficient to maintain normal carbon dioxide tensions. Two of the patients with cardiogenic shock had also elevated carbon dioxide tensions suggesting that similar mechanisms are operative in both cardiogenic shock and left ventricular failure. The identification of patients with respiratory acidosis is important as therapy with intermittent positive pressure ventilation will correct the acidosis. Estimation of blood gases should be part of a routine service for patients

with shock or failure complicating acute myocardial infarction.

MacKenzie et al. (1964) had shown that patients with acute myocardial infarction with shock had a significant metabolic acidosis. Neaverson (1966) examined 50 consecutive cases of acute myocardial infarction, admitted to the Barnet General Hospital. He showed that 60% had a significant base deficit and the more severe the base deficit, the more likely were there to be complications. In the present study, patients with uncomplicated myocardial infarction did not have a metabolic acidosis. The patients with left ventricular failure had a mixed pattern some with a respiratory alkalosis and some with a mixed respiratory and metabolic acidosis. The patients with cardiogenic shock all had a marked metabolic acidosis. Kirby, and McNicol (1966) reported the acid-base status in 123 patients with acute myocardial infarction. In 28 patients the pH was less than 7.35. In 24 of these 28 patients, the acidosis was associated with a fall in plasma bicarbonate; in the remaining 4 it was with an increased carbon dioxide tension. Blood lactic acid levels were raised in patients with hypotension and left ventricular failure. In the present study, lactic acid levels were only measured in patients with cardiogenic shock, the mean level was 4.79 mmol/l with a range of 1.64 to 12.9 mmol.l. In studies, not yet reported, of patients with hypoxaemia from differing causes, we have only found lactic acid levels above the upper limit of normal (1.74 mmol.l) in patients with cardiogenic shock. Weil and Afifi (1970) have recently

shown that lactate alone serves as a reliable indicator of the severity of shock from varying causes and that neither lactate pyruvate ratio nor excess lactate improve the prognostic index. The increased lactic acid must be produced by tissue hypoxia, but reduction in cardiac output may also cause a reduction in hepatic blood flow so that the normal uptake of lactate by the liver is reduced or even reversed (Berry, 1967). Studies of regional blood flow and of liver function in patients with low output states complicating acute myocardial infarction, can determine the precise role of the liver in the shock states. Future therapeutic approaches might then be directed to improving specific organ blood flow.

Patient TA merits special comment. This patient was a known mild diabetic controlled on phenformin. Whilst convalescing from a slight cerebro-vascular episode, she developed central chest pain. On admission to hospital she had all the clinical features of shock. Her electrocardiogram showed an anterior intramural myocardial infarction. Blood gas analysis revealed a severe metabolic acidosis (pH 6.95, pCO_2 19 mm Hg). Her blood lactic acid was 6.42 mmol/l. Blood sugar was 228 mg 100 ml, and there was no ketonuria. This patient did not have diabetic ketoacidosis but the role of phenformin in the development of her severe metabolic acidosis must be questioned. The precise mode of action of this drug remains unclear, but what is certain is that it promotes lactic acid production. The drug interferes with cellular aerobic metabolism, perhaps by inhibition of cytochrome oxidase or of NAD dependent

oxidative phosphorylation (Oliva, 1970). Since 1962, 18 cases have been described with clinically severe lactic acidosis occurring in phenformin treated patients. Most of the patients were in shock or had other recognised causes of lactate overproduction. It has been suggested that phenformin may aggravate the lactic acidosis, occurring in patients with shock (Bernier, Miller and Springate, 1963). In the present case the precise role of phenformin in uncertain, but the metabolic acidosis in this patient was much greater than in the other patients with cardiogenic shock.

Mixed venous oxygen saturation was reduced in all but 2 patients below the normal level of 70% suggested by Zimmerman (1966). The lowest mixed venous oxygen saturations were found in those patients with left ventricular failure and cardiogenic shock. These findings are in agreement with previous reports of the correlation of venous oxygen saturation with clinical condition (Goldman, Klughaupt, Metcalf, Spivack and Harrison, 1968, Scheinman et al. 1969). In patients with cardiogenic shock, the low levels of mixed venous oxygen saturation ($S\bar{v}O_2$) were recorded when the patients were breathing high flow oxygen. It is likely that $S\bar{v}O_2$ would be lower still in these patients in the absence of oxygen therapy.

Goldman et al. (1968) suggested that although central venous oxygen saturation reflected the clinical condition of the patient, it could not be used to predict the cardiac output. The data in this study suggests a close relationship between cardiac output and mixed

venous oxygen saturation. The measurement of cardiac output may not be a practical procedure in the majority of units caring for patients with acute myocardial infarction, but pulmonary arterial catheterization by the float technique is a relatively simple and safe procedure. This allows the measurement of mixed venous oxygen saturation and provides a rational basis for management of patients with shock or failure complicating acute myocardial infarction using the minimum of equipment.

THE EFFECTS OF DIGOXIN, ACID-BASE CORRECTION AND VOLUME LOADING IN CARDIOGENIC SHOCK

CHAPTER IV

The findings reported in the previous chapter give a basis for devising an appropriate therapeutic regime for the management of cardiogenic shock. As the most striking haemodynamic finding was of increasing left ventricular failure with increasing degrees of clinical severity, therapy to correct cardiac failure would seem appropriate. Digitalis was first suggested for the treatment of severe grades of acute myocardial infarction by Herrick (1912). Levine and Brown (1929) recommended digitalis for those with manifest congestive failure but held that it was best avoided in most cases as it was 'more likely to do harm than good'. Fishberg et al. (1934) also warned of the dangers of digitalis and postulated that it could cause increased irritability of the heart, increased liability to embolisation and coronary artery vaso-constriction. They also held that it might increase the force of systolic contraction and predispose to rupture.

The view held by Goodman and Gilman (1965) is of interest. "Digitalis is contra-indicated during the first few days following acute coronary thrombosis. The clinical picture is usually one of shock rather than congestive failure and digitalis by further decreasing the cardiac output, may make the patient worse". Of the standard text books in cardiology, Hurst and Logue (1970) emphasise that the altered physiology in cardiogenic shock is poorly understood, but recommended that digitalis should be given in the

early stage of shock. Freidberg (1966) states that the value of digitalis in shock is not established and requires further study. In both text books digitalis is advocated for left ventricular failure complicating acute myocardial infarction. In the current edition of Paul Wood's Diseases of the Heart and Circulation (1968) it is suggested that digitalis should be used for conventional heart failure, but makes no mention of it in the management of shock in acute myocardial infarction.

The haemodynamic effects of digitalis preparations in cardiogenic shock were first studied by MacKenzie (1965), He reported on the administration of digoxin to 6 patients with uncomplicated myocardial infarction and 4 patients with shock. In the patients with uncomplicated myocardial infarction, intravenous digoxin increased a previously impaired cardiac output. In contrast the drug had no effect when cardiac output was within the normal range. Little haemodynamic benefit was demonstrated when digoxin was administered to the 4 patients with cardiogenic shock. He postulated that the coincidental metabolic acidosis blocked the usual cardiotonic effect of digoxin. An appropriate therapeutic approach might combine correction of the metabolic acidosis with the administration of digoxin.

If therapy with digoxin and acid base correction were unsuccessful, it might then be argued that cardiogenic shock was not an extreme example of left ventricular failure, as therapy known

to improve the failing heart (Mason and Braunwald, 1967), had been without effect. Several possibilities exist; the damage to the left ventricle might be so great that the heart can no longer respond to the cardiotonic action of digoxin; an alternative view is that of Nixon et al. (1966) and Ross (1967) when they held that cardiac asynergy might be improved by increasing left ventricular volumes.

A therapeutic schedule was therefore devised in which patients with cardiogenic shock were digitalized, their metabolic acidosis was corrected and if there was no improvement they were given a fluid load. This chapter describes the results obtained.

PATIENTS AND PROCEDURES: Five of the patients with cardiogenic shock described in Chapter III were studied. The patients were given high flow oxygen and if pain was present, this was relieved by opiates.

After a control period of 15 minutes, digoxin (0.75 to 1.0 mg) was given slowly intravenously. The variation in dose was conditioned by a clinical assessment of the weight of the patients. Metabolic acidosis was corrected using either sodium bicarbonate or the amine buffer Tris (hydroxymethyl) amino-methane (THAM). If there had been no haemodynamic or clinical response to digoxin after a minimum time of one hour, volume expansion was undertaken. This was done in an identical manner to that described by Nixon et al. (1966). Approximately 200 ml of 5% laevulose was given rapidly intravenously. If there was no response a further 200 ml of laevulose was given.

One patient had been digitalized prior to the study and in this patient only the response to volume loading was studied, one patient died before volume expansion was undertaken. A summary of the therapeutic schedule is shown in Table 10.

During the study vascular pressures and electrocardiogram were monitored continuously. Cardiac output determinations were made at 5 minute intervals. Arterial oxygen and carbon dioxide tension and pH were measured at 15 minute intervals.

RESULTS:

1. Digoxin and Acid-Base Correction:

The individual haemodynamic and metabolic responses to therapy with digoxin and acid-base correction are shown in figs. 16, 17, 18 and 19.

In the 2 patients given bicarbonate, the acidosis was corrected but neither the correction of the acidosis nor the administration of digoxin produced any marked change in haemodynamic or clinical state. In particular there was no significant change in cardiac output or stroke volume and heart rate was little affected. There was an increase in carbon dioxide tension after the administration of the bicarbonate (+ 9 mm Hg and + 14 mm Hg).

In the 2 patients given THAM the metabolic acidosis was corrected with little change in arterial carbon dioxide tension. There was however, a marked fall in arterial oxygen tension after THAM

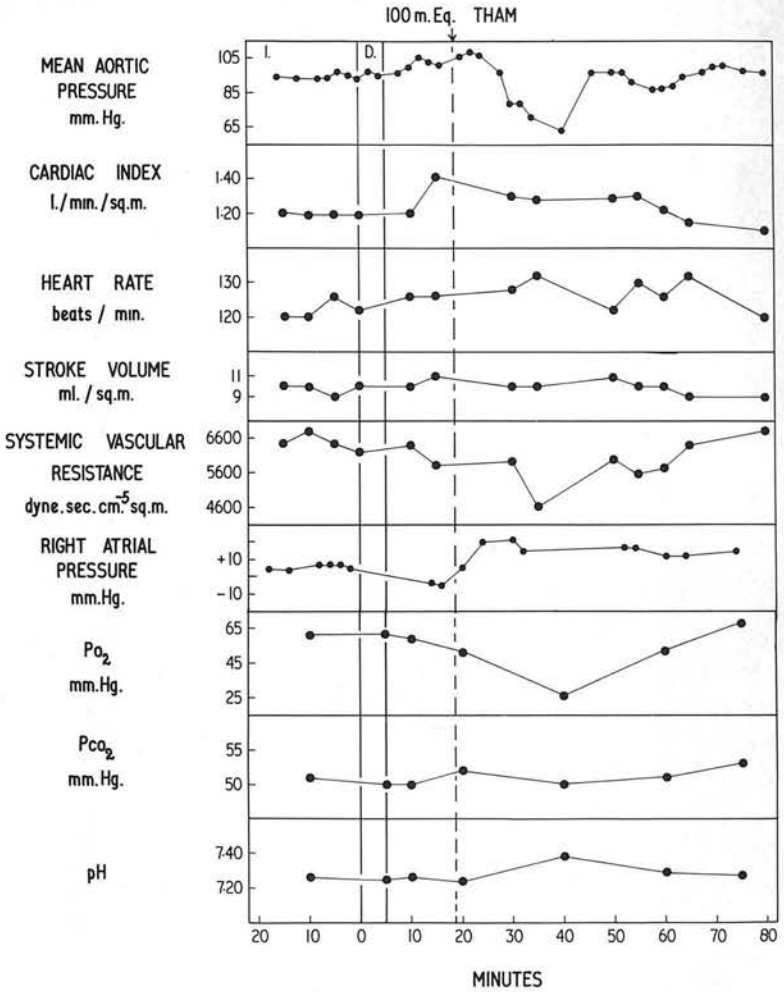


Fig. 16

Patient TU: Circulatory and metabolic response to intravenous digoxin (0.75 mg) and THAM. Digoxin was administered intravenously over a period of five minutes.

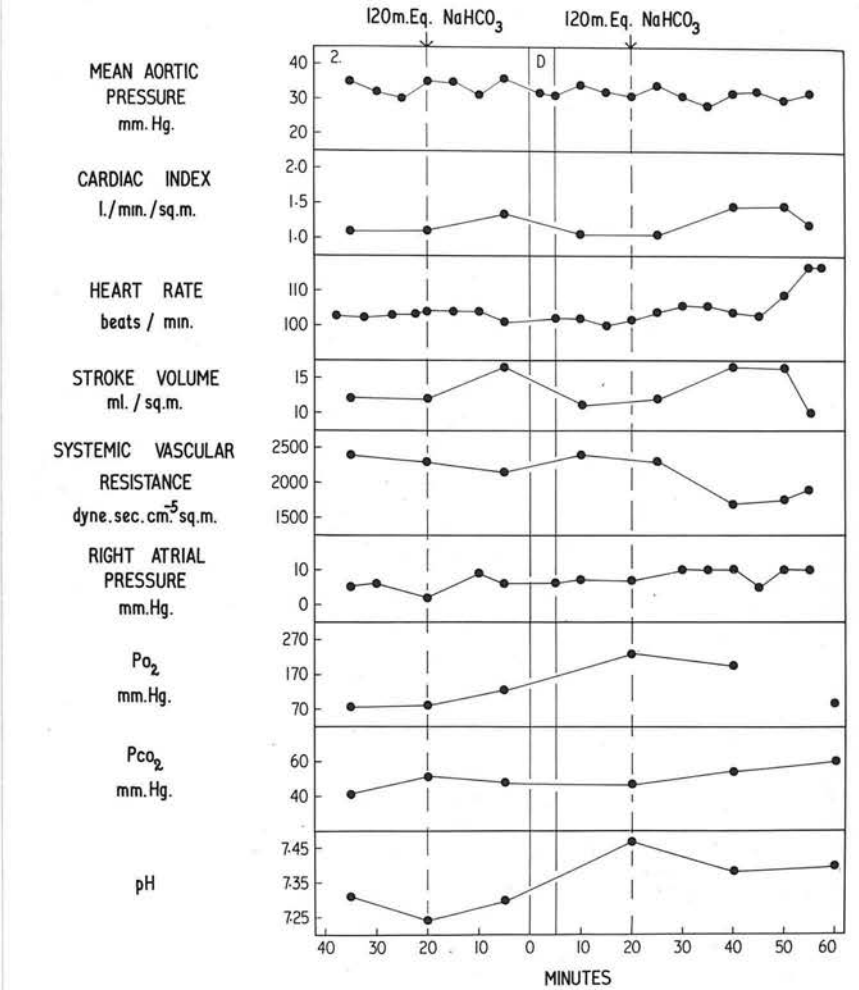


Fig. 17

Patient PL: Circulatory and metabolic response to intravenous digoxin (1.0 mg) and sodium bicarbonate.

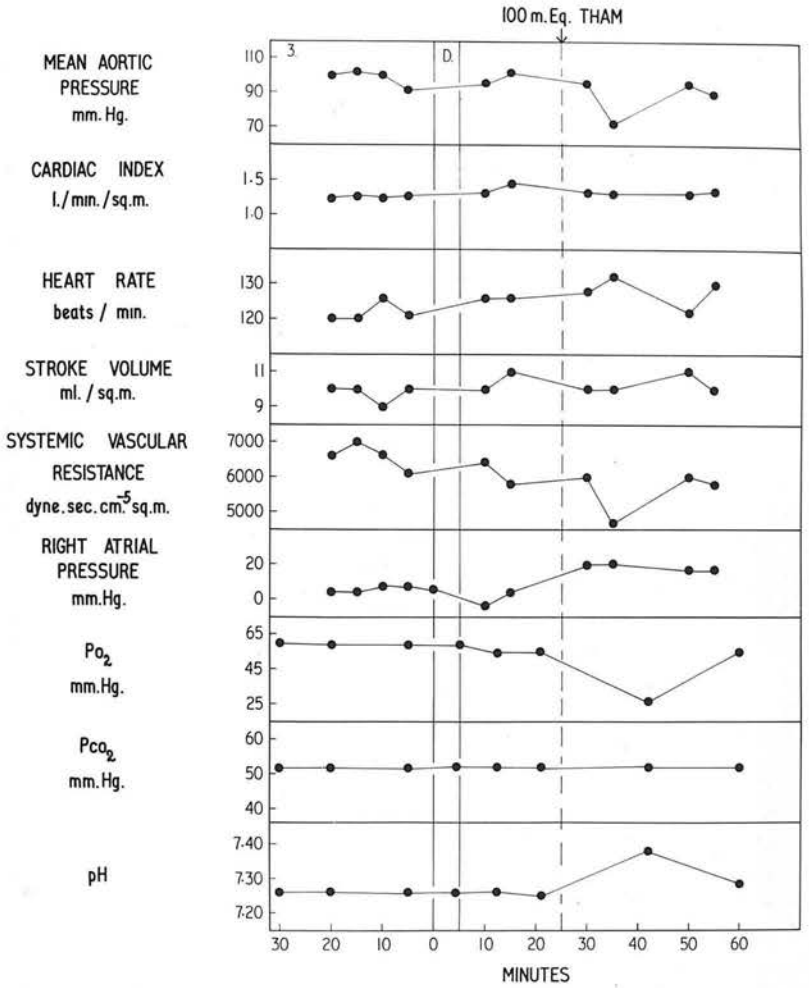


Fig. 18

Patient A1: Circulatory and metabolic response to intravenous digoxin (0.75 mg) and THAM.

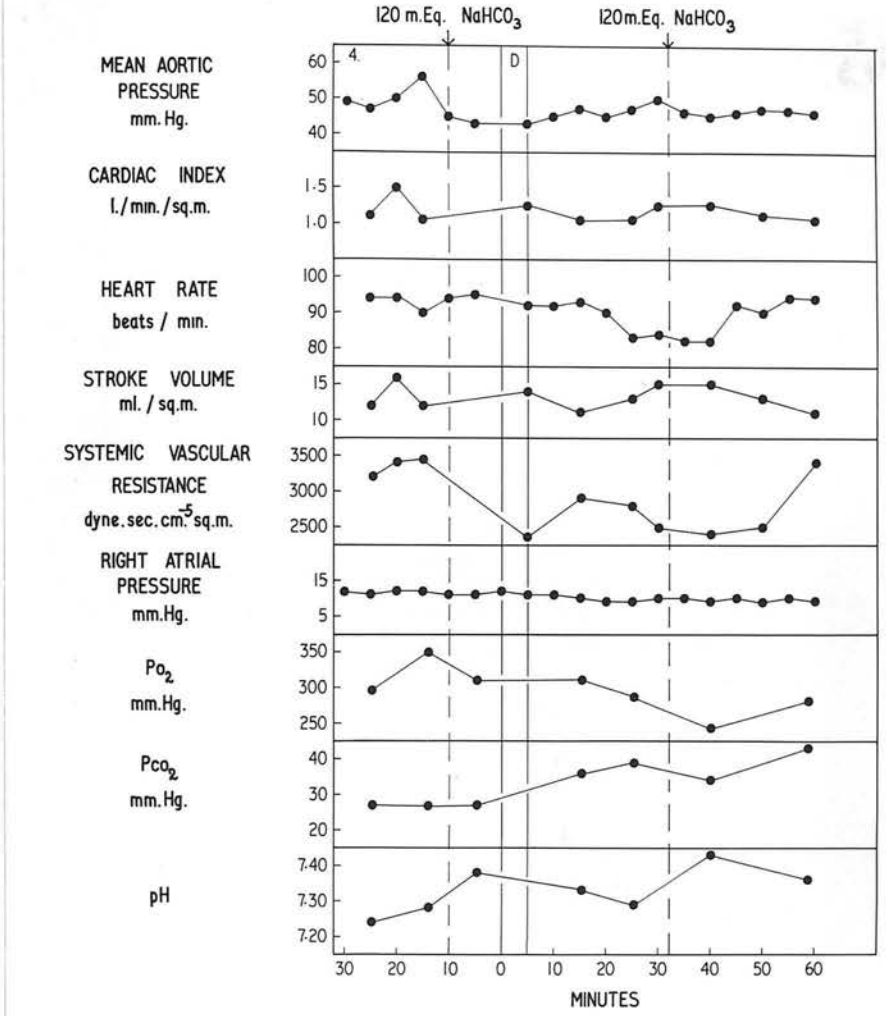


Fig. 19

Patient L1: Circulatory and metabolic response to intravenous digoxin (0.75 mg) and sodium bicarbonate.

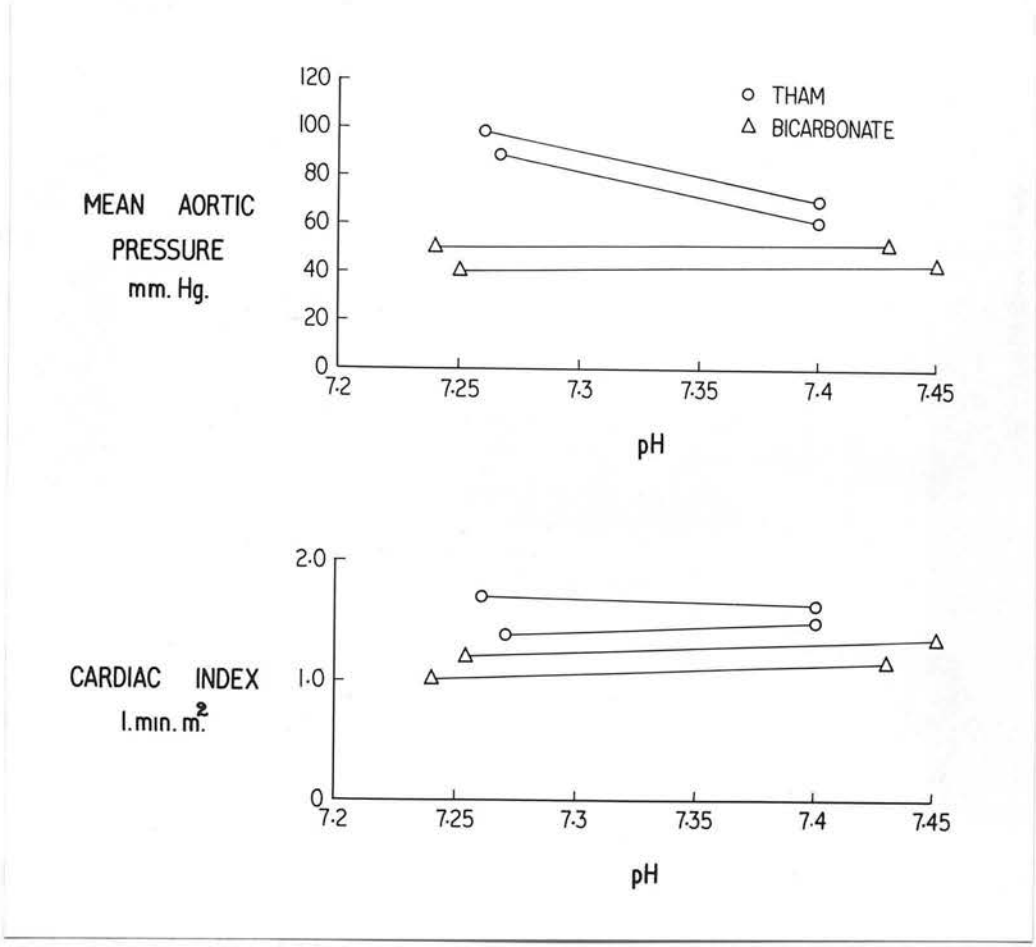


Fig. 20

Mean aortic pressure and cardiac output in cardiogenic shock before and after therapy with digoxin and sodium bicarbonate or THAM.

(-36 mm Hg, - 32 mm Hg). At the same time there was a fall in systemic arterial blood pressure with little change in cardiac output or stroke volume. Right atrial pressure increased in both patients given THAM.

The hypotensive and hypoxic effects of THAM persisted for approximately 10 minutes, making precise interpretation of the effects of digoxin difficult. However, in neither patient was there a sustained increase in cardiac output, stroke volume or systemic arterial pressure.

Whether the metabolic acidosis was corrected by sodium bicarbonate or by THAM the decrease in hydrogen ion concentration was short lived and within 20 to 30 minutes, the pH had returned to pre-treatment levels.

The effects of acid-base correction and administration of digoxin on cardiac output and systemic arterial pressure are summarised in fig. 20.

2. Volume Loading:

Individual haemodynamic responses to therapy with 5% laevulose are shown in figs. 21, 22, 23 and 24. After the administration of laevulose to patient TU, there was a rise in right atrial pressure from 3 mm Hg to 9 mm Hg, but the mean systemic arterial pressure fell from 63 mm Hg to 40 mm Hg and at the same time the pulse pressure was narrowed. Heart rate increased by 15 beats per minute

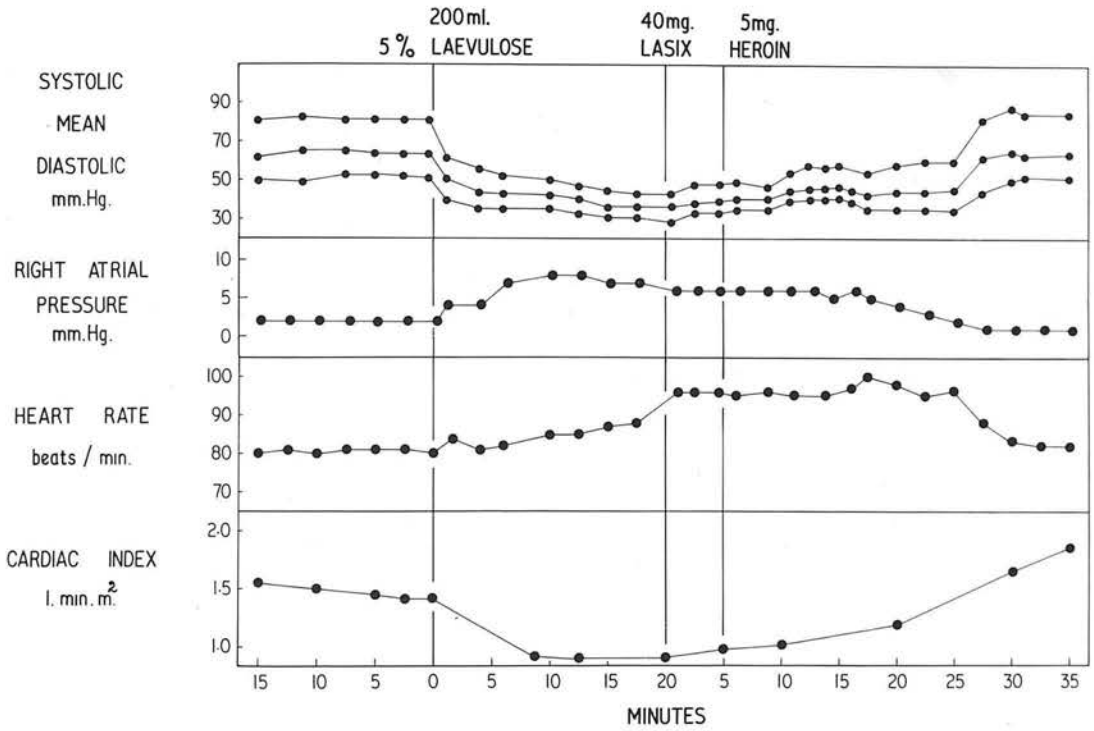


Fig. 21

Patient TU: Circulatory response to 200 ml 5% laevulose.

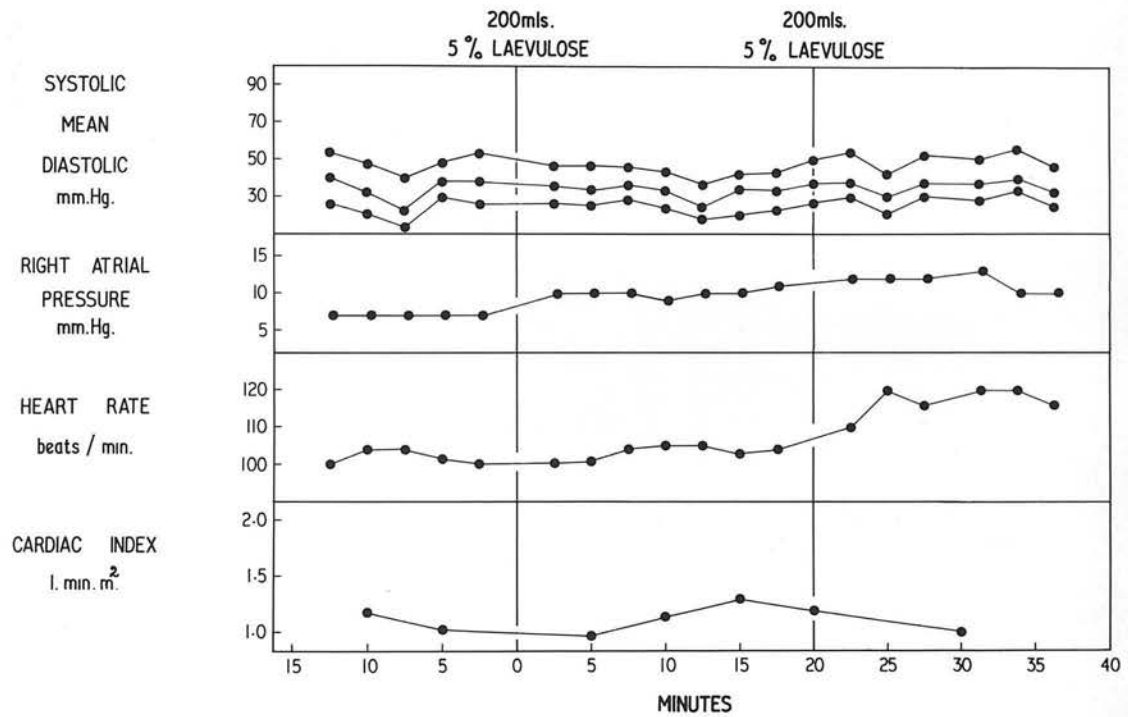


Fig. 22

Patient PL: Circulatory response to 400 ml 5% laevulose.

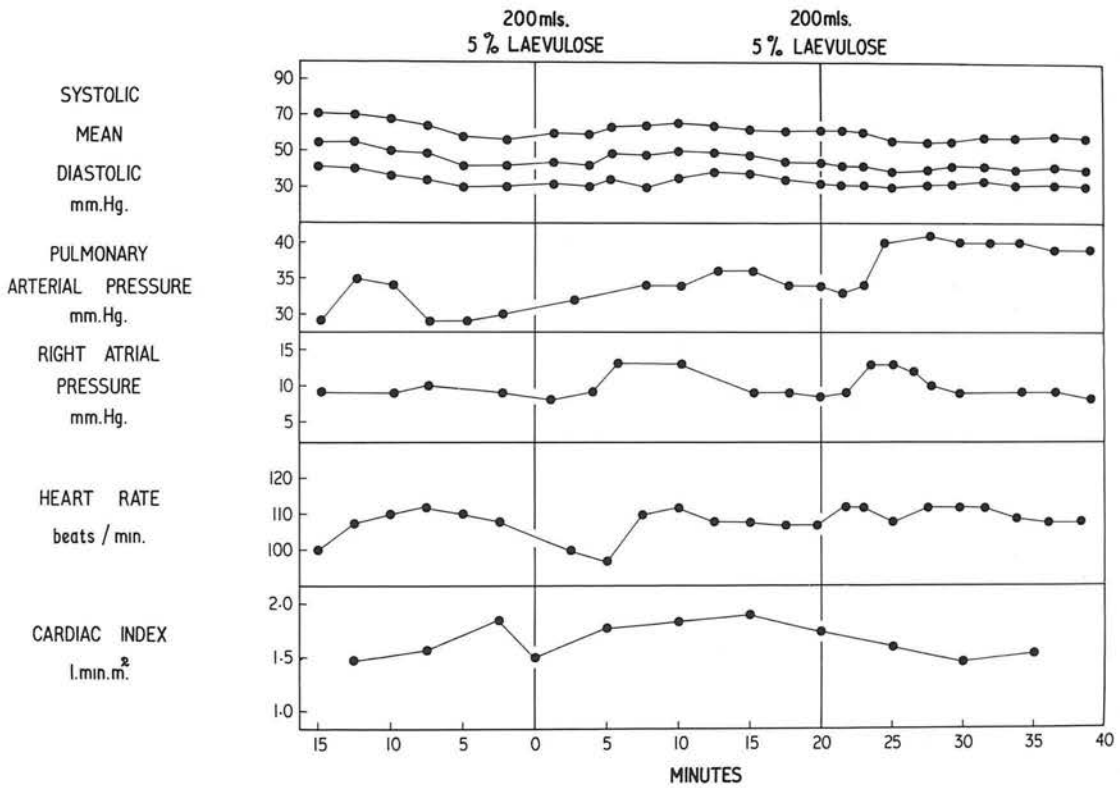


Fig. 23

Patient LA: Circulatory response to 400 ml 5% laevulose.

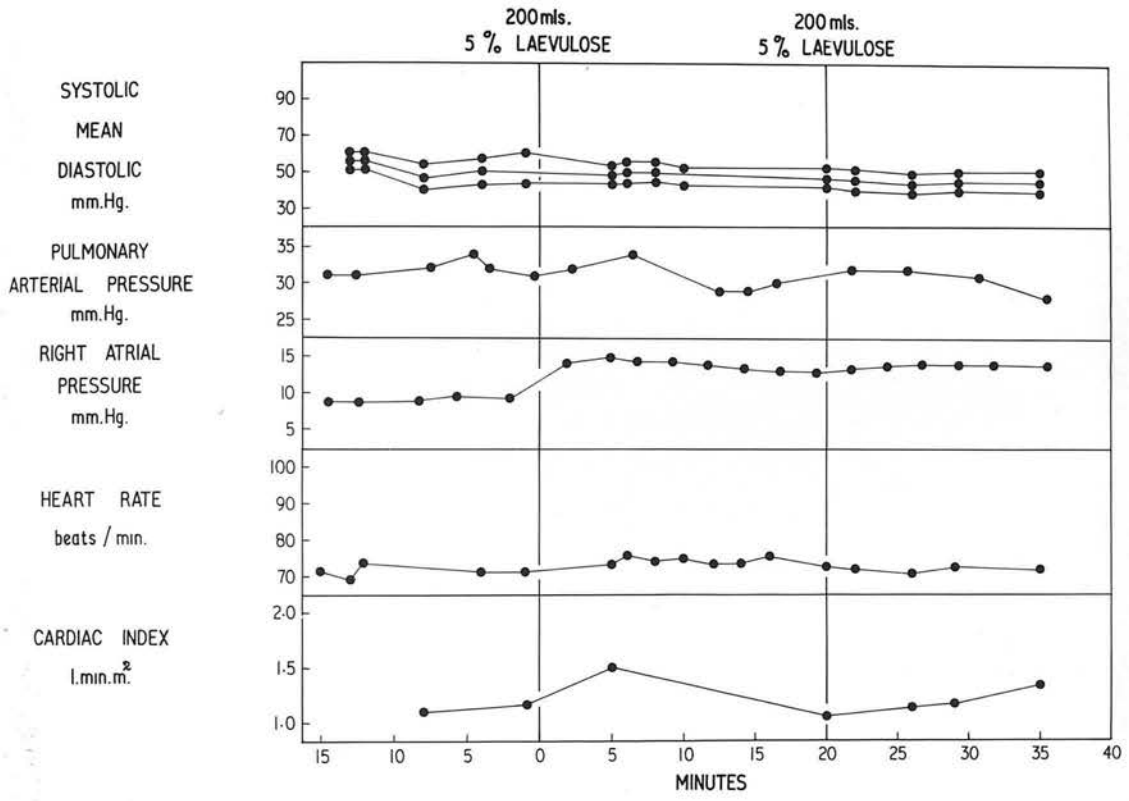


Fig. 24

Patient Ll: Circulatory response to 400 ml 5% laevulose.

following the laevulose and cardiac output fell by 0.5 litres.min.m^2. Thus the calculated stroke volume was severely reduced from 18 ml.m^2 to 11 ml.m^2. With the deterioration of haemodynamic function there was a marked worsening of the clinical condition. The patient became breathless and more confused. On auscultation there were widespread crepitations throughout both lung fields. Fortunately both the clinical and haemodynamic effects were reversed by the intravenous administration of 5 mg. heroin and 40 mg. of frusemide (lasix).

In the other 3 patients the administration of laevulose brought about neither a clinical deterioration nor a clinical improvement. After the infusion of laevulose there was an increase in right atrial pressure. There was also an increase in pulmonary arterial pressure. In patient LI, pulmonary arterial pressure rose from 32 mm Hg in the control period to 40 mm Hg after the infusion was completed. But despite the increase in filling pressures, there was little change in cardiac output or systemic arterial pressure.

DISCUSSION

Acid-Base Correction and Digoxin

The precise influence of metabolic acidosis on cardiac performance is in dispute. It has been demonstrated that increasing hydrogen ion concentration of the circulating fluid reduces cardiac contractile strength in submammalian species (Burridge 1912, Daly

and Clark 1921, Lorković 1966) and in isolated mammalian heart lung preparations (Gremels and Starling 1926, Thrower, Darby, Aldinger, Tenney and Westbrook 1959, Ng, Levy and Zieske 1967). The effect of metabolic acidosis on intact mammalian preparations and in man is variable. Rocamora and Downing (1969) demonstrated in cats that, with sympatho-adrenal function intact, metabolic acidaemia failed to diminish myocardial contractility. In a survey of the literature, they concluded that as long as there was normal sympathetic function changes in pH produced little change in myocardial contractility. However, there was a break point below which changes in pH could produce altered cardiac function. Moreover there was a species difference, thus the cat could tolerate reduction in pH to 6.80 whilst the dog could only tolerate reductions in pH to 7.10.

There are few well documented reports of the effects of metabolic acidosis on myocardial function in man. Reid, Enson, Harvey and Ferrer (1965) studied the effects of variations in the blood pH upon the electrocardiogram in patients with pulmonary disease. The pH of the patients was altered by administering hydrochloric acid, THAM or sodium bicarbonate. The range of pH achieved was 7.30 to 7.64 but no variation in the electrocardiogram was noted. Kirby and McNicol (1966) attempted correction of 6 patients with metabolic acidosis complicating acute myocardial infarction but although they had "some success" there was no effect on mortality. Neaverson (1966) corrected the metabolic acidosis of

12 patients with acute myocardial infarction and was able to document an increase in systolic blood pressure in all patients. There was no mention of how blood pressure was measured and no further details of the patients were given.

Downing, Talner and Gardner (1966) had shown that in newborn lambs, the combination of hypoxia and metabolic acidosis caused a decrease in myocardial contractility that was at least partially reversed by sodium bicarbonate. Metabolic acidosis alone or hypoxia alone did not cause a decrease in myocardial contractility. The severe hypoxia present in patients with cardiogenic shock might then aggravate the effects, if any, of the metabolic acidosis. But the patients described by Kirby and McNicol (1966) and the patients presented in this thesis, were breathing oxygen and their arterial hypoxia was at least partially corrected, and yet there was little evidence of improvement in myocardial function.

Robin and Bromberg (1953) have pointed out the necessity of not oversimplifying Claude Bernard's concept of the internal environment, since different body compartments are separated by semi-permeable membranes which limit the passage of ionized particles such as $/\bar{}H^{+}\bar{}/$. Thus the correction of an extracellular acidosis may have little effect on intracellular pH; the lack of demonstrable response to sodium bicarbonate might be explained on this basis, and it was to try to correct intracellular pH that THAM was used.

THAM was first used to control environmental pH in fish

transport. Nahas (1959) noted that THAM reversed rapidly the failure of the isolated heart induced by perfusing the heart with elevated carbon dioxide mixtures, this effect could not be obtained by sodium bicarbonate or lactate. Robin, Wilson and Bromberg (1961) studied the kinetics by which THAM leaves the extracellular compartment and concluded that THAM penetrates cell membrane rapidly. Because of the rapid penetration of the intracellular space and because it is a sodium free hydrogen ion acceptor, THAM seemed an ideal buffer for correcting metabolic acidosis in cardiogenic shock. However, in this study the use of THAM produced further hypotension and markedly decreased arterial oxygen tensions despite oxygen therapy in the 2 patients given the amine buffer. Vick, Hinshaw and Spink (1961) had noted its hypotensive action in endotoxin induced shock in dogs and although THAM increased urine flow and pH in their experiments, it did not increase survival. They concluded that because of its hypotensive effect THAM might actually be detrimental in endotoxin shock. The depression of ventilation that occurs after the use of THAM was emphasised by Brinkman, Brunswick and Whitehouse (1961). They noted in patients with respiratory acidosis a decrease in arterial oxygen tension after THAM and there was a reduction in respiratory minute volume. The effect of THAM on ventilation during correction of metabolic acidosis does not seem to have been well documented. In the 2 patients with cardiogenic shock treated with THAM minute ventilation was not measured but carbon dioxide tensions were little changed despite the reduction in arterial oxygen tensions. This

would argue an increased shunt effect in the lungs rather than a primary depression of ventilation: little change was noted in cardiac output so that any shunt effect would be by alteration in perfusion to the lung. More precise interpretation would require detailed cardiorespiratory studies of the effects of THAM. In practical terms the hypotension and hypoxaemia following the use of THAM suggests it has little value in the correction of metabolic acidosis after myocardial infarction.

Metabolic acidosis in cardiogenic shock probably represent such severe circulatory insufficiency that relieving arterial hypoxia and the correction of the extracellular acidosis has little influence on intracellular oxygen tension and pH in ischaemic areas of the myocardium. Assuming that the combination of hypoxia and metabolic acidosis decreases myocardial function in man, then only by restoring a physiological milieu to the ischaemic areas of the heart surrounding the infarcted areas will normal function be restored. With diseased coronary arteries, a low cardiac output and low coronary artery filling pressures, it is unlikely that a normal physiological milieu can be restored and abnormal cellular metabolism will persist. It is for this reason that many workers have explored various forms of mechanical circulatory assistance for the management of cardiogenic shock (Birtwell, Soroff, Ruiz, Many and Deterling 1969). With mechanical assistance at least cardiac output and coronary artery filling pressures can be increased.

It is also valid to consider whether alterations in acid-base status could alter the action of drug therapy in shock. Weil, Houle, Brown, Campbell and Heath (1957) reported in abstract form that the pressor response to vaso-pressors was diminished by acidosis. Mason and Braunwald (1967) have reviewed the effects of digitalis. The action of digitalis is to exert a positive inotropic effect by a direct enhancement of myocardial contractility. The fundamental mechanisms by which the cardiotonic actions of digitalis are mediated at cellular level remain to be precisely elucidated. At present there is not yet a full understanding of the processes involved in normal contraction. It appears likely that intracellular ionic transport underlies the coupling of the excitation-contraction response (Mason, Spann and Zelis 1969). The presence of active calcium in the region of the myofilaments appears to be intimately associated with the initiation of the contractile process (Nayler 1967). Digitalis compounds probably alter the rate of calcium exchange and augment the myoplasmic concentration of calcium. Mason et al. (1969) suggested that cardiac glycosides might ultimately provide more calcium ions for the contractile process by a direct influx or by a glycoside induced influx of sodium ions displacing calcium from sarcoplasmic reticulum. Digitalis may inhibit the cell membrane pump ATPase and thus the sodium-potassium pump mechanism operative in diastole, resulting in less efficient return of potassium into the cell.

Whatever the precise mechanism of action of digitalis, its action is closely related to ion transport. In metabolic acidosis normal cell physiology must be altered and ion transport disturbed. It seems reasonable to suppose that the action of a drug which acts by influencing ion movement will be disturbed in metabolic acidosis. In this context then, it is disappointing that no beneficial effects of acid-base correction and administration of digoxin were noted in the 4 patients with cardiogenic shock. The same strictures about inadequate intracellular correction of the acidosis and inadequate relief of hypoxia are valid, in addition there may be inadequate distribution of digoxin because of poor coronary perfusion. However, the failure of digitalization and acid-base correction to improve clinical or haemodynamic function in cardiogenic shock suggests severe left ventricular damage.

What then is the place of digoxin in acute myocardial infarction? The haemodynamic studies of MacKenzie (1965) had suggested that in patients with a low cardiac output without shock, digitalization improved circulatory status. Malmcrona, Schröder and Werko (1966) studied 10 subjects with recent transmural infarction who were treated with intravenous lanatoside C (0.8 mg) and found an increase in arterial pressure but no significant change in cardiac output. Balcon, Hoy and Sowton (1968) studied 11 patients with recent acute myocardial infarction: only 2 patients had radiographic evidence of pulmonary venous congestion and the highest recorded mean pulmonary

arterial pressure was 19 mm Hg. After the intravenous injection of 0.25 mg acetyl beta strophanthidin (7 cases) or 0.5 mg digoxin (4 cases) they noted a fall in cardiac output (14%) with no change in pulmonary arterial pressure, aortic pressure or peripheral resistance.

Apart from the studies reported in this thesis and by MacKenzie (1965), haemodynamic effects of digitalization in cardiogenic shock have also been reported briefly by Gunnar, Loeb, Pietras and Tobin (1970). In a review article on the haemodynamic effects of myocardial infarction and the results of therapy they showed in diagrammatic form the results of digitalization in patients in shock with acute myocardial infarction in 12 patients, 8 of whom were simultaneously receiving an infusion of noradrenaline. In only one patient did cardiac output increase by more than 15% and the average change from the control levels was -6%. In most patients central venous pressure was reduced but changes in systemic arterial pressure were variable. No further details were given but the authors concluded that digitalis should be given to patients with cardiogenic shock. Braunwald (1970) has suggested from experimental work that digitalis increases oxygen demand of the heart and that in dogs with cardiogenic shock the administration of digoxin caused an increase in the size of the infarcted area. However, claims about oxygen consumption of the heart must be viewed with caution. For in heart failure, the reduction in size of the failing heart brought about

by digitalis may lower the heart's demand for oxygen more than the direct effect of the agent on contractility increasing oxygen demand (Covell, Braunwald, Ross and Sonnenblick 1966).

The reports of other experimental studies are almost as confusing. Cronin and Zoster (1965) studied the effects of rapid digitalization in dogs with experimental cardiogenic shock. They reported a significant rise in arterial blood pressure and cardiac output with a reduction in left ventricular end-diastolic pressures. The administration of noradrenaline raised cardiac output at the expense of a further elevation in left ventricular end-diastolic pressure. In contrast to this Hood, McCarthy and Lown (1967) studied dogs with experimental myocardial infarction and concluded that acetyl strophanthidin caused no improvement in left ventricular function. Marano, Kline, Cestero and Kuhn (1966) produced shock in dogs by microsphere embolization. The administration of ouabain produced a significant rise in cardiac output and arterial pressure. Left ventricular function, as judged by changes in the maximum rate of pressure rise in the left ventricle (dp/dt) was also increased. No such changes were found in control animals without infarction.

Although there is no satisfactory account of the action of digitalis in patients with left ventricular failure complicating acute myocardial infarction, it is probably in this group that digitalization will be most effective. Beneficial effects in an uncomplicated group may be difficult to demonstrate with

conventional techniques; where improvement in clinical and haemodynamic state in the so-called uncomplicated group occurs after digitalis therapy, it is likely that underlying cardiac failure had not been noted. The haemodynamic studies demonstrated in Chapter III emphasise that in a considerable number of patients, left ventricular failure is difficult to diagnose without the aid of radiological and haemodynamic investigations.

For the physician having to treat cardiogenic shock without the aid of bedside physiological information, it would seem wise to regard the situation as one of masked left ventricular failure and to administer digitalis. Although the haemodynamic studies reported here and those reported by MacKenzie (1965) failed to demonstrate any beneficial effect of digoxin in cardiogenic shock, the studies were carried out on patients with unequivocal shock. The studies reported in Chapter III suggest there is an increasing degree of left ventricular disorder with increasing clinical severity and there is no sharp distinction between patients with severe left ventricular failure and cardiogenic shock. Although studies are needed to demonstrate any potentially beneficial effects of digitalis in patients with left ventricular failure, at the present time it would seem correct to administer digoxin to patients with cardiogenic shock. By improving left ventricular contractility an adequate cardiac output might be obtained. An adequate cardiac output would correct tissue hypoxia and reverse the metabolic acidosis. Although

it seems probable that in most patients with cardiogenic shock the damage to the ventricle is so great that digitalization cannot improve cardiac function, individual patients may have a satisfactory response to digitalis therapy. The hazards of digitalis excess must be carefully considered, but the frequency of digitalis induced arrhythmias seems to be no greater than in other cardiac emergencies requiring its use (Askey 1951).

Volume Expansion

The report of low left ventricular pressure in cardiogenic shock by Nixon (1968) and the successful response to therapy with volume expansion reported by Nixon and his colleagues (1966, 1967, 1968a, b, c) and by Swan et al. (1969) have suggested that a number of patients could be improved by volume expansion. The precise number is uncertain. Allen, Danzig and Swan (1967) reported in abstract form on the incidence and significance of relative hypovolaemia as a cause of shock associated with acute myocardial infarction. In 29 patients with cardiogenic shock, right atrial pressure was measured, in 14 of those patients the right atrial pressure was less than 10 cm H_2O. However, Cohn, Khatri and Hamosh (1969) reported again in abstract form, a study of left ventricular pressure in 22 patients with either cardiogenic shock or pulmonary embolism. In all patients with cardiogenic shock, left ventricular end-diatolic pressure was elevated (range 12 to 44 mm Hg) even when the central venous pressure was normal. The rapid deterioration of patient TU with a small volume load (200 ml) suggests that this patient was precipitated into

frank pulmonary oedema by the therapy. This patient had a low right atrial pressure (5 mm Hg) and although pulmonary arterial pressure was not obtained during volume expansion, this had been measured during digoxin therapy and was only slightly elevated (21 mm Hg). This patient then had the lowest right sided pressures of the patients treated with volume expansion but it was in this patient that the therapy caused such a dramatic deterioration. The other patients treated with laevulose showed neither clinical deterioration nor improvement, but the increase in pulmonary arterial and right atrial pressure without an increase in cardiac output or systemic arterial pressure were strong indications that these patients were in extreme left ventricular failure. When changes in venous pressure are plotted against changes in cardiac output, a very flat response is obtained (fig. 25). By reference to the data of Sarnoff and Berglund (1954), the response obtained is that of the failing heart and in patient TU the decrease in cardiac output with increase in right atrial pressure indicates that the downslope of the Starling curve has been reached (Patterson and Starling 1914). In these patients there is absolutely no evidence of hypovolaemia.

A large number of clinical reports of intravenous therapy in cardiogenic shock have not shown any alteration in the relief of shock and the mortality rate was no better than with non-specific therapy (Epstein and Relman 1949, Sampson and Singer 1949, Cochran 1952, and Binder, Ryan, Marcus, Mugler, Strange and Agress 1955). The absence of any noted beneficial effect of volume expansion in

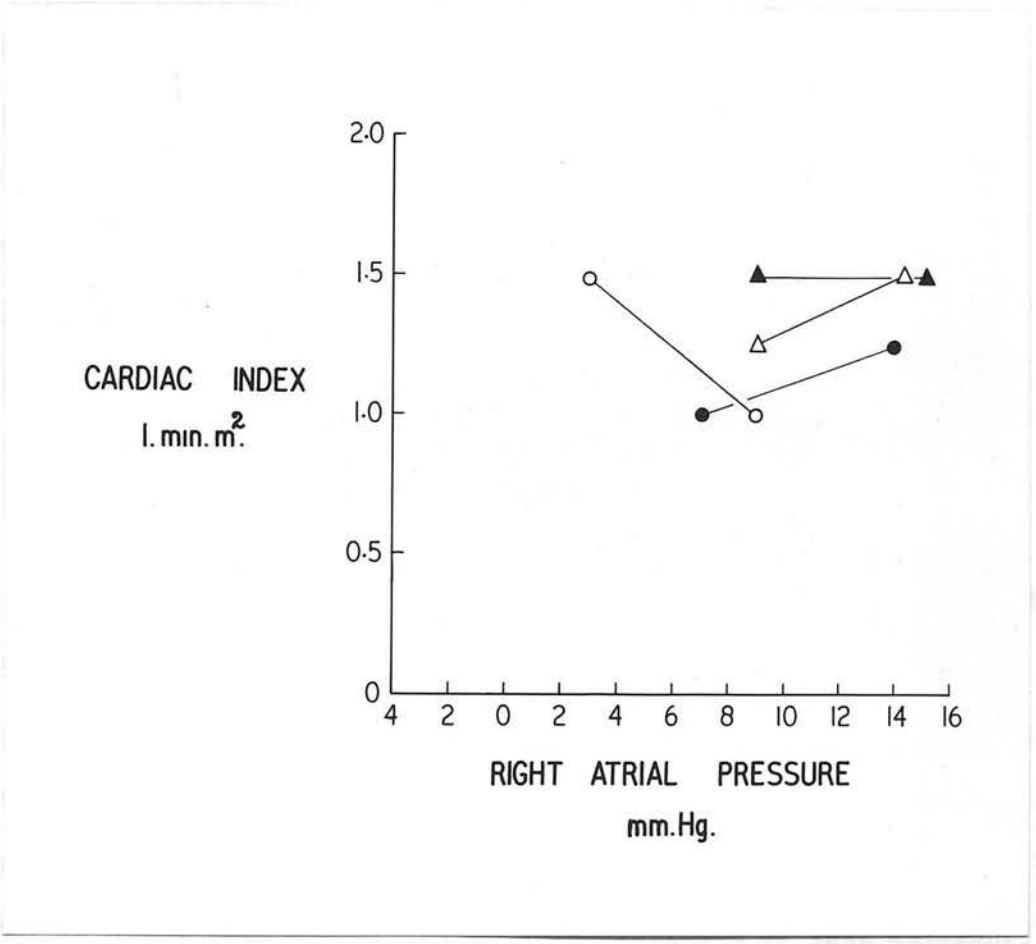


Fig. 25

The change in cardiac output with increments in right atrial pressure in cardiogenic shock.

such a large number of patients suggests the number of patients who might respond to volume loading therapy is small. Nevertheless, volume depletion might occur where patients have been previously taking diuretic therapy, where there has been profuse sweating or diarrhoea or where infarction has occurred after major surgery. There may also be loss of fluid from intravascular compartment at the time of circulatory arrest. As no well documented haemodynamic studies of volume depletion in acute myocardial infarction have been made there is an urgent need for more information about left heart pressures in cardiogenic shock.

A Starling (function) curve of a ventricle does not reflect the state of all the fibres of that ventricle. Ischaemic areas and infarcted areas of the heart must operate on different function curves (Harrison 1965). Gorlin, Klein and Sullivan (1967) reported an angiographic study of 100 patients with coronary artery disease. Twenty-four patients manifested abnormal movements of the left ventricle which they classified as akinesis (lack of wall movement) and dyskinesis (paradoxical wall movement). Akinesis was present in 16 and dyskinesis in 8 patients. Contrary to expectation, aneurysms composed solely of thin-walled fibrotic areas occurred in only 7 of 16 patients observed directly at necropsy or surgery. Krohn, Dunne, Magidson, Hanish, Tsuji, Redington and Kay (1968) reported an angiographic study of 20 cases of arteriosclerotic and valvular heart disease. During systole a limited portion of the ventricular wall failed to contract properly. The paradoxical bulge

was also recorded by the electrical impedance cardiogram, which measures changes in electrical resistance in the thorax related to instantaneous changes in heart shape. In left ventricular failure the apex dilated paradoxically in systole. In the La Place relation the intracavitary pressure would equal the muscle tension divided by cavity radius. Because of the abnormal increase in the radius at the apex the thin apical muscle would have to contract almost as strongly as the base to sustain intracavitary pressure. But this interpretation of the La Place equation must be accepted with some reservation; the law applies to situations in which the thickness of the wall is negligible in comparison to the radius of curvature,

Studies of left ventricular function in experimental acute myocardial infarction (Pairolero, McCallister, Hallerman and Ellis 1970) have shown a measurable decrease related to the size of the infarct. It is likely that an asynergic area develops in most cases with acute myocardial infarction. In the majority this causes only minor changes in left ventricular function, in some however, akinesis or dyskinesis is more marked and probably contributes to the left ventricular failure of cardiogenic shock.

Ross (1967) has argued that when ventricular filling pressure is relatively normal or even moderately elevated a depressed ventricle can operate on the ascending portion of its Starling curve. He therefore advocated volume expansion to try to make optimum use of the intrinsic mechanism for augmenting the force and extent of fibre

shortening. Nixon et al. (1966) suggested that the infusion and elevation of venous pressure had acted beneficially in his cases by distending the ventricle to the point at which its output maintained life.

That the elevation of venous pressure brought about no improvement in cardiac output of the patients presented in this chapter, does not suggest that ventricular dyskinesis or dysynergy is unimportant in cardiogenic shock. Indeed the concept of localised left ventricular dysfunction in cardiogenic shock needs detailed study, for it is possible that some patients could be improved by an immediate surgical approach involving surgical excision or plication (Milstein 1970). But the lack of response to therapy with digoxin, acid-base correction and volume loading suggests that in the patients so treated, the left ventricular damage was so great that the heart could no longer respond to any therapeutic measure. The rapid production of pulmonary oedema in one patient emphasises the dangers of treatment with volume expansion in cardiogenic shock and also emphasises that shock and failure in acute myocardial infarction are very much part of the same response to ventricular damage.

CIRCULATORY EFFECTS OF MORPHINE IN ACUTE MYOCARDIAL INFARCTION

CHAPTER V

INTRODUCTION

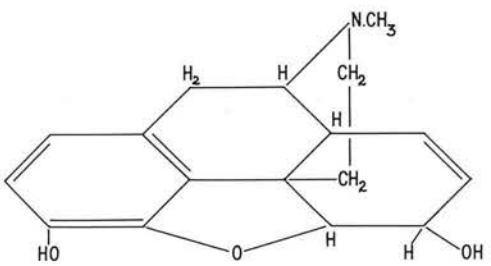
The use of opium as a medicament dates back to antiquity. The Papyrus Ebers (approximately 2,000 B.C.) mentions the power of opium to obtund pain. Poppy juice was referred to in the writings of Theophrastus in the third century B.C. Galen employed opium to relieve pain and opiates were used by Arabian physicians in the dark and middle ages. By the middle of the sixteenth century, opium was widely used in Western Europe. Paracelsus (1490-1540) is credited with naming the extractive preparation, tincture of opium, Laudanum from the Latin 'laudo' I praise. By 1680 the English physician Sydenham had written that of the drugs to relieve suffering 'none is so efficacious as opium'. The history of opium in antiquity has been reviewed by Macht (1915).

However, it was not until the isolation of morphine from opium by Sertürner in 1806 that pharmacological studies on opiates commenced. He administered his 'morphium' to dogs and described its narcotic effect. Despite the isolation of many other alkaloids during the following century, morphine remains the chief member of the group and is the standard for comparisons with newer analgesics.

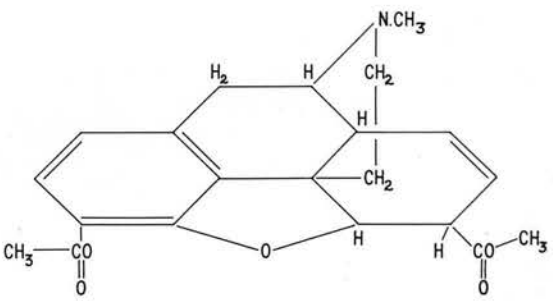
Opium is defined by Martindale's Extra Pharmacopeia as 'the dried or partly dried latex obtained by incising the unripe capsules of Papaver somniferum (Fam. Papaveraceae)'. The pharmacologically

active constituents are alkaloids. The main alkaloids in opium are of the phenanthrene chemical class and consists of morphine, codeine and thebaine. Morphine is by far the most important alkaloid of opium. It chemical structure was first proposed by Gulland and Robinson in 1925 and confirmed by total synthesis by Gates and Tschudi (1952). Its structure is shown in fig. 26. Many of the derivatives of morphine are made by the introduction of relatively simple chemical radicals into the hydroxy groups of the morphine molecule. Thus heroin (diacetyl morphine) is synthesized by acetylation of both hydroxy groups. Codeine is methylmorphine, the methyl substitution being on the phenolic OH. Small substitutions of this nature can produce compounds with very different pharmacological actions emphasising the importance of both the phenolic and alcoholic hydroxy groups (Beckett 1952).

The pharmacology of opiates has been extensively studied and there exists a number of comprehensive reviews (Kreuger, Eddy and Sumwalt 1941, Reynolds and Randall 1957, Eckenhoff and Oech 1960). The actions of opiates upon the cardiovascular system have received less attention than have the effects on respiration. Most authorities are agreed that the main consequence of administration of an opiate on the circulation is to produce hypotension. There are clinical reports of hypotension occurring after all narcotics and these have been summarised by Eddy, Halbach and Braenden (1957). Of more practical significance would be a comparison of the incidence



MORPHINE



HEROIN

Fig. 26

The chemical structure of morphine and heroin (diacetyl morphine).

of hypotension produced by the various opiates. However, comparative data is lacking and few narcotics have been tested in a manner which allows comparison (Eckenhoff and Oech 1960). The main reason for lack of comparative data has been the minimal response in normal volunteers unless some stress was laid on the circulation. To date, the commonest stress used when assessing the action of opiates has been a gravitational one using a 'tilt-table'. Drew, Dripps and Comroe (1946) using a tilt-table demonstrated that 12-30 mg of morphine intramuscularly produced marked hypotension in 76 degrees head-up position. Bandaging the legs lessened the hypotension. The authors concluded that morphine led to peripheral vascular dilatation and dilatation of the capacitance vessels. Similar results were reported by King, Elder and Dripps (1952) using pethidine in hospitalized patients.

Although morphine has been recommended for the relief of pain following acute myocardial infarction ever since the early clinical description of the syndrome (Herrick 1912 and Moor 1930), little attention has been focussed on its cardiovascular actions in this disease. In 1965 Thomas and his colleagues administered morphine sulphate (3 to 10 mg) to 13 patients with acute myocardial infarction and studied the haemodynamic effects. Two of the patients were studied twice. Cardiac output was measured using a dye dilution technique with Coomassie blue dye as the indicator; changes in dye concentration were measured by a photoelectric earpiece. Their information was presented in graphical form and

precise interpretation is difficult. In 7 instances, cardiac output was unchanged and in 8 patients cardiac output was decreased. In 2 patients the initial cardiac output was greater than 10 litres per min. Changes in heart rate were variable but in 2 patients the heart rate slowed and in one of those the heart rate slowed to 20 beats per min. A fall in blood pressure was recorded in 8 patients and in one patient the systolic pressure fell to 30 mm Hg but with a concomitant bradycardia. No statistical analysis of the data was undertaken. Using values from their graphical data, the fall in blood pressure for the group is not statistically significant when assessed by a paired 't' test. Although the authors were cautious in the interpretation of their data, this single study has been widely quoted since as adequate evidence that morphine can produce marked hypotension in acute myocardial infarction.

Two years later in a study from this department, we examined the circulatory effects of heroin administered to 8 patients with recent myocardial infarction (MacDonald, Rees, Muir, Lawrie, Burton and Donald 1967). There was a mean fall in aortic pressure of 5 mm Hg after the administration of heroin. This fall in blood pressure achieved statistical significance at the 5% level but cardiac output, systemic vascular resistance, heart rate, stroke volume, right atrial and pulmonary arterial pressures showed no significant trend. These studies suggested that heroin might be preferable to morphine in the relief of pain following acute myocardial infarction. However, the data was not strictly comparable

as dosage levels and investigational techniques were dissimilar. In the search for a more suitable analgesic agent for use in myocardial infarction, we have also examined the circulatory effects of pethidine (Rees, Muir, MacDonald, Lawrie, Burton and Donald 1967). This was found to produce a biphasic action on the circulation with an initial rise in mean systemic pressure (+12 mm Hg) followed in 10-15 minutes by a fall to a mean pressure 10 mm Hg below the control level. There was also a rise in systemic vascular resistance and heart rate in the first 10-15 minutes and then a fall in these variables below control levels. This was in accord with previous data from normal subjects (Prescott, Ransom, Thorp and Wilson 1949). It seemed that pethidine was an unsuitable analgesic to administer after a recent myocardial infarction and that in our experience heroin was preferable.

The recent increase in the number of heroin addicts in the U.K. encouraged us to try to determine more precisely whether heroin had any major advantages over the more standard regime of morphine. The present study was undertaken to make a thorough assessment of the circulatory side effects of these two opiates in myocardial infarction. Because of the inherent difficulties in algesimetric methods, no attempt was made to assess their capacity to relieve pain.

General Outline

The study was conducted in two parts. In the first instance, the circulatory effects of 10 mg of morphine were examined in 8

patients with recent myocardial infarction. This study was conducted in an identical manner to that of the previously reported heroin study (MacDonald et al. 1967). A further 3 patients received an antihistaminic drug, cyclizine, prior to the administration of morphine. These studies are reported in this chapter.

As these studies showed no important difference between the effects of morphine and heroin a second more detailed study was undertaken in which the effect on blood pressure, heart rate and blood gases of heroin and morphine administered on a 'blind' basis to 27 patients with recent myocardial infarction were studied. This study is reported in Chapter VI.

THE CIRCULATORY EFFECTS OF MORPHINE

Methods:

The personal characteristics and clinical details have been listed in Table 3, but for convenience are grouped together in Table 11.

Eleven patients were studied, all had sustained an acute myocardial infarction as judged by World Health Organisation (1959) criteria within the previous 36 hours. The patients were all in sinus rhythm and were not shocked nor in clinical heart failure. No patients had received any drug therapy within the 12 hours preceding the investigation. The investigations were conducted with the patients in their own beds in the clinical investigation and therapy area. The patients were studied lying supine in bed with one pillow supporting the head. Control observations were made in each patient over a period of 20 minutes. In 8 patients, 10 mg of morphine diluted in 10 ml of saline was then injected intravenously over a period of 5 minutes and observations were continued for a further 60 minutes. In addition 3 patients were treated with antihistamines prior to the administration of morphine; 50 mg of the antihistaminic drug, cyclizine, was administered intramuscularly 20 minutes prior to the injection of 10 mg of morphine.

The electrocardiogram was recorded continuously throughout the study. Systemic arterial, pulmonary arterial and right atrial pressure recordings were interrupted only for the sampling of

arterial and mixed venous blood. Cardiac output determinations were made at 5 minute intervals throughout the study.

A paired 't' test was applied to the differences between the mean values during the control period in each patient and the measurements recorded at 5, 10, 20, 30, 40 and 50 minutes after the start of the injection, the null hypothesis being that the difference would be zero.

Comparison of Circulatory Effects of Morphine with those of Heroin: The results obtained after the administration of morphine were compared with our results, previously reported, of those patients who had received heroin (MacDonald et al. 1967). This paper is included in the appendix. In the heroin study 2 patients had been studied in a tilted position and they are excluded from the present comparison. The results of observations following the administration of heroin to 2 further patients have been included in the heroin group to bring the number of patients in each group to 8.

Where there was any distinct circulatory effect following either morphine or heroin, this was predominantly in the early period (0-10 minutes). In a few instances there was a more gradual change with the effects only being marked after some 10 minutes had elapsed. Therefore for the purposes of the comparison of the circulatory effects of the 2 opiates have been divided arbitrarily into early (0-10 minutes) and late (11-60 minutes) periods. In both periods the maximum positive or negative percentage changes from the

control levels produced by each drug were compared with one another using 'Student's' 't' test.

RESULTS

Clinical Effects: After the injection of morphine, 2 of the patients fell asleep and remained asleep for the rest of the study, while the other patients became drowsy. Flushing was not noted in any patient and the slight sweating which had been prominent after treatment with heroin was not seen after therapy with morphine. No other undesirable side effects were observed.

Circulatory Changes Following Morphine: The sequential changes in the circulatory measurements for each patient are shown in figs. 27, 28, 29 and 30 and the mean changes for the group in Table 12.

Mean Arterial Pressure: In 7 patients mean arterial pressure fell in the early period (0-10 min). In 5 patients the fall was less than 10 mm Hg but at the 5th minute, mean arterial pressure had decreased by 14 mm Hg in patient 2 and 18 mm Hg in patient 8. In patient 7 the mean arterial pressure rose by 12 mm Hg at the 5th minute. The changes for the group were not significant ($p > 0.05$).

Changes in the late period (11-60 minutes) were variable and showed no significant trend. In 3 patients (2, 4 and 7) arterial pressure was lower than in the control period.

Cardiac Output: In 7 of the patients cardiac output increased soon after the administration of morphine. The maximum increase was

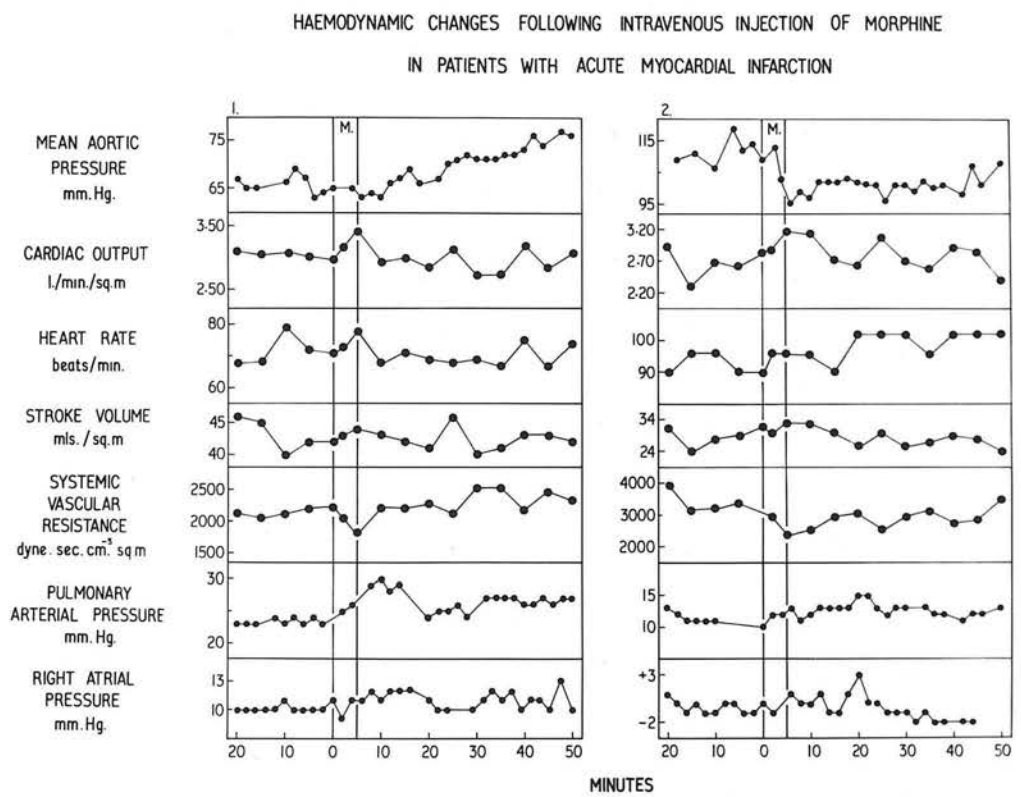


Fig. 27

The circulatory effects of morphine in two patients with acute myocardial infarction. (DA and WH).

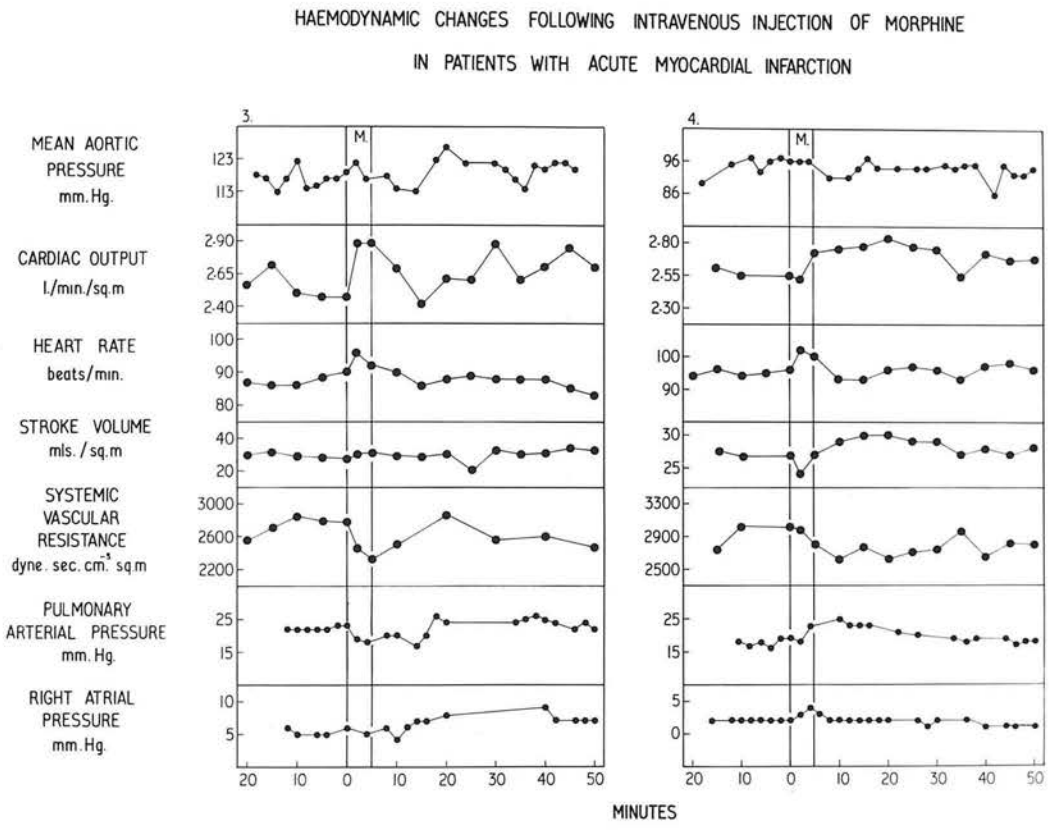


Fig. 28

The circulatory effects of morphine in 2 patients with acute myocardial infarction (AR and McL).

0.49 $l.min.^{-1}m^{-2}$ in patient 2 and this was observed at the 5th minute. In patient 6 the cardiac output fell immediately by 0.52 $l.min.^{-1}m^{-2}$. For the group there was no significant change in cardiac output in the early period following the administration of morphine ($p > 0.05$).

In the late period cardiac output declined to levels similar to those of the control period. In patient 6, the initial reduction in cardiac output was continued in the late treatment period. However, there was no statistically significant difference between the control period and the late treatment period ($p > 0.05$).

Systemic Vascular Resistance: In 7 of the 8 patients, the calculated systemic vascular resistance ($p < 0.05$) decreased immediately. In patient 2, the fall was of 1050 $dyne.sec.^{-1}cm.^{-5}m^{-2}$ (30%) below that of the control period. After the initial period, systemic vascular resistance tended to increase to control levels. In patient 6, the calculated resistance increased following the administration of morphine and remained elevated throughout the study.

Heart Rate and Stroke Volume: The mean increase in heart rate after the administration of morphine was 5 beats/min (range -3 - + 10 beats/min) ($p < 0.01$). As cardiac output also increased, no increase in stroke volume was observed. Changes in heart rate and stroke volume in the later part of the study were small.

Mean Right Atrial Pressure: The right atrial pressure in the control period ranged from 0-11 mm Hg. No consistent trend was apparent after the administration of morphine.

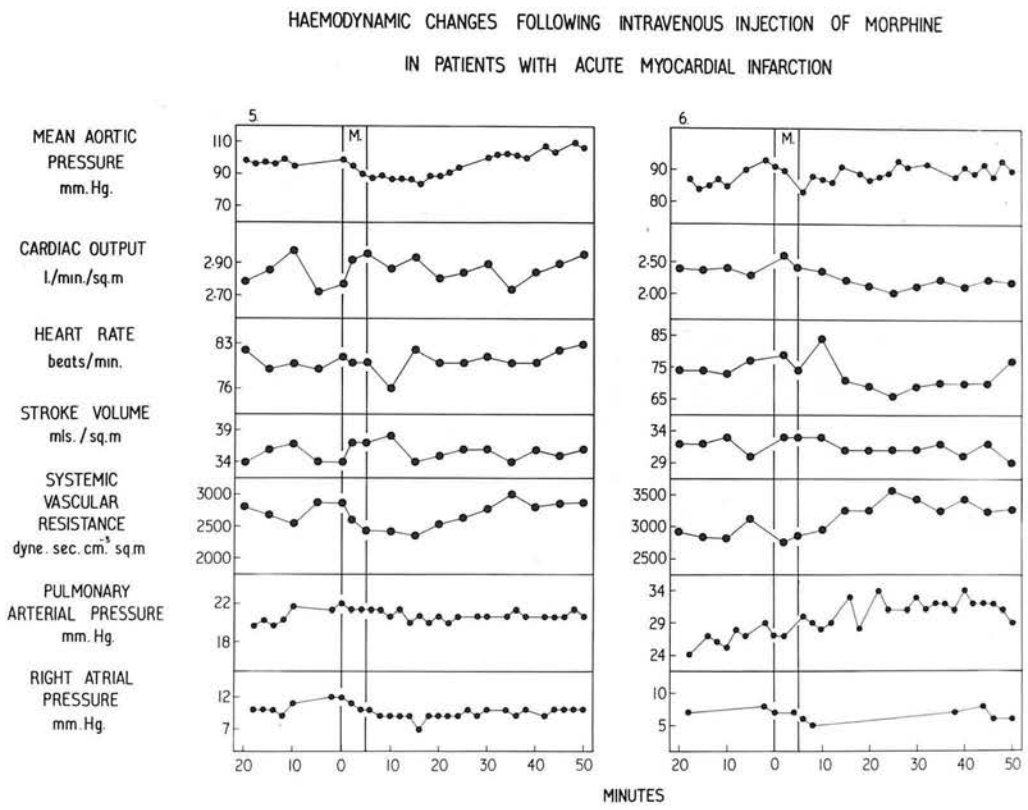


Fig. 29

The circulatory effects of morphine in two patients with acute myocardial infarction. (DI and FR).

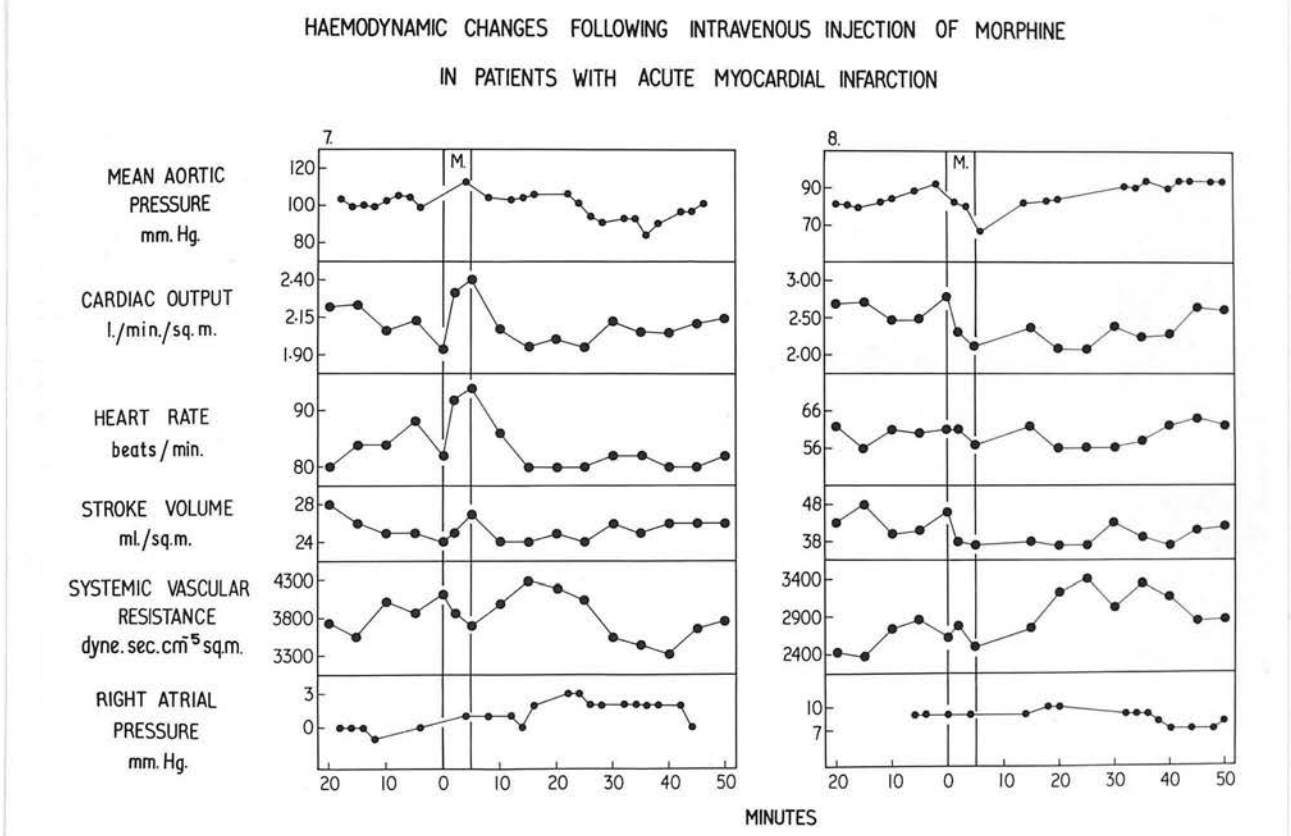


Fig. 30

The circulatory effects of morphine in two patients with acute myocardial infarction. (TH and ST).

Mean Pulmonary Arterial Pressure: The average mean pulmonary arterial pressure was 20 mm Hg (range 11-27 mm Hg). After the administration of morphine, there was a small rise in pressure; this was significant at the 20th and 30th minutes ($p < 0.02$).

Cyclizine and Morphine: Of the 3 patients who were pre-treated with cyclizine prior to the administration of morphine, the circulatory changes were very similar to those patients who had not been pre-treated with cyclizine. Cyclizine itself produced a rise in mean arterial pressure but did not prevent a fall in pressure following the use of morphine (fig. 31). In one patient (no. 10) there was an initial rise in pressure after the administration of morphine before the production of hypotension.

Comparison of the Circulatory Effects of Morphine and Heroin:

The results detailed above are compared with our own data from the published heroin study (MacDonald et al. 1967) and are depicted diagrammatically in fig. 32. The maximum change in the variable examined is shown for each patient in both early (0-10 mins) and late (11-60 mins) periods.

Early Effects: Both drugs produced a small fall in systemic arterial pressure. The changes were more marked in the patients who received morphine but no statistical difference could be demonstrated between the 2 groups ($p > 0.05$). After the administration of opiates there was a significantly greater increase in cardiac output ($p < 0.05$) in those patients who received morphine when compared with those who

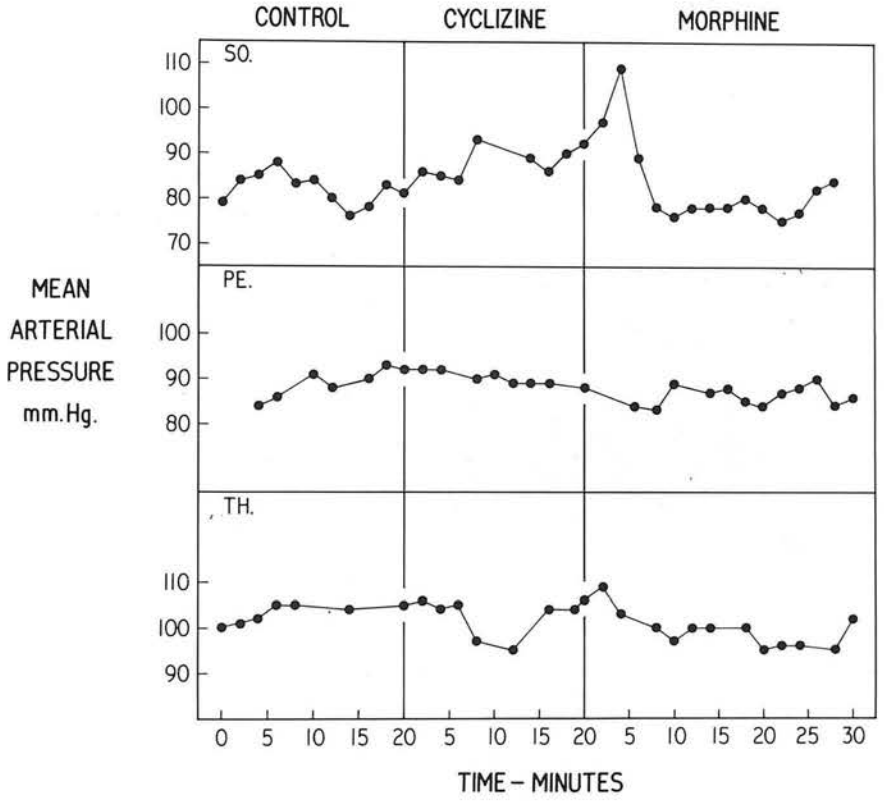


Fig. 31

Mean aortic pressure in 3 patients with acute myocardial infarction treated with cyclizine and morphine. (Patients SO, PE and THO).

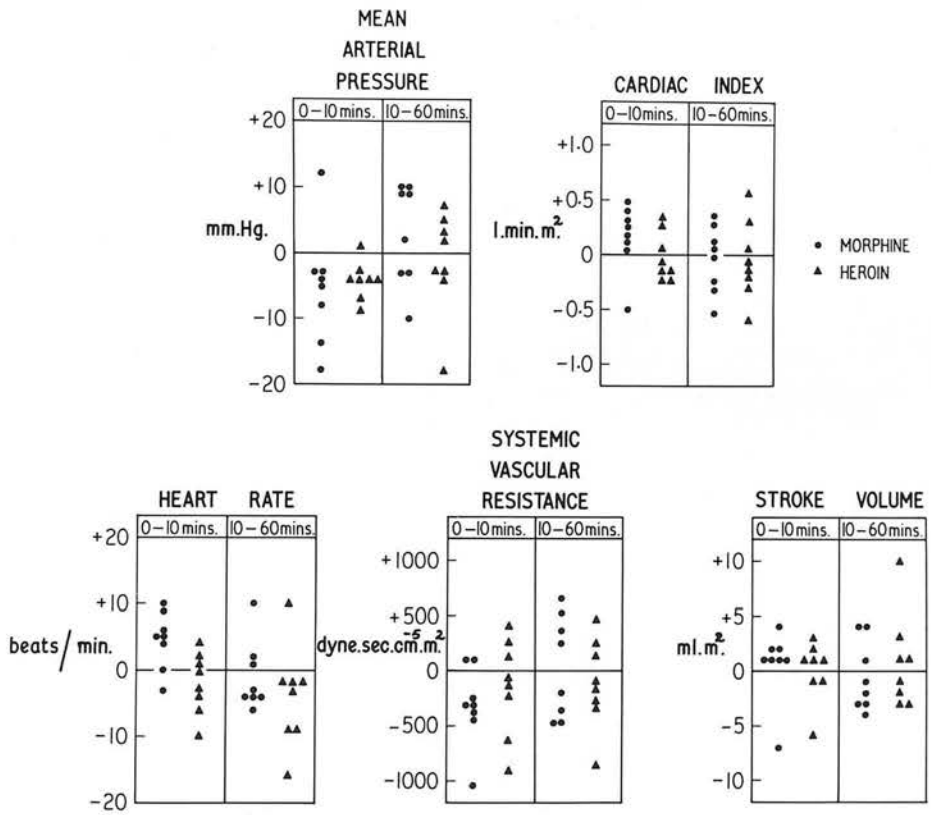


Fig. 32

Comparison of the maximal circulatory changes after morphine with maximal changes after heroin (morphine n = 8; heroin n = 8).

The circulatory effects of heroin have been published (see appendix).

had heroin. The increase in heart rate was also significantly greater in the group who received morphine when compared with the heroin treated group ($p < 0.01$).

Late Effects: There was no significant difference between the effects of the 2 opiates in the late period.

DISCUSSION

The present study confirms that there are variable circulatory effects following the administration of morphine. Amongst the early effects lasting some 5-10 minutes, the trend was for the mean aortic pressure to fall and the cardiac output and heart rate to rise. These findings are similar to those of Thomas et al. (1965) but in no patient in the present study was there a profound fall in blood pressure. Sapru (1966) measured the changes in the circulation following a bolus injection of 15 mg of morphine in normal subjects, patients with mitral valve disease and patients with left ventricular failure. In the immediate period in nearly all patients and normal subjects, there was an increase in cardiac output, this being largely rate dependent. There was also a decrease in systemic vascular resistance, although arterial pressure only decreased in those patients with left ventricular failure. He postulated that this group could be under increased sympathetic stimulation and the relief of the symptoms produced a reduction in sympathetic discharge. The fall in systemic vascular resistance suggested that morphine produced vasodilatation in some or all of the vascular bed. Furthermore, morphine produced a fall in the calculated cardiopulmonary blood volume. The redistribution of blood could account for the therapeutic efficacy of morphine in left ventricular failure.

In the present study no attempt has been made to analyse the

changes in cardiopulmonary blood volume because the injection site used for the introduction of indocyanine green was in one of the great veins and varied from patient to patient and might even vary during the study of one patient. Changes in pulmonary arterial pressure showed no overall consistent trend, but where the mean pulmonary arterial pressure was greater than 25 mm Hg the pressure was reduced following the administration of either morphine or heroin. This finding is in accordance with Fejfar, Bergman, Fejfarova and Valach (1957) and Sapru (1966) and lends support to the idea that opiates cause redistribution of total blood volume in left ventricular failure.

The hypotension after opiates has also been attributed to histamine liberation. Opiates do have the ability to release histamine (Feldberg and Paton 1951). Clinical observers have noted weals along veins into which opiates have been injected (Eckenhoff and Oech 1960). In dogs anaesthetised with pentobarbital and then given meperidine (pethidine) there was a steep fall in blood pressure (Van Arman and Sturtevant 1958). Blood samples taken at the lowest point of fall were found by guinea pig tests to contain large amounts of histamine. The antihistamine drug diphenhydramine blocked the hypotension occurring with meperidine, but histamine could still be found to be present. However, in the present study when the antihistamine drug, cyclizine, was given to 3 patients prior to the administration of morphine there was still a slight

opiate induced fall in mean arterial pressure. The circulatory effects of opiates in man are too variable to make firm conclusions but it does seem that histamine liberation is not the universal mode of causing circulatory depression.

Direct myocardial depression has also been invoked as a mechanism producing hypotension following opiates (Schmidt and Livingston 1933). Subsequent workers (Pur-Shahriari, Mills, Hoppin, and Dexter 1967) suggested that although the maximum rate of pressure rise of the left ventricle (dp/dt) decreased after morphine the decreases paralleled the decrease in left ventricular end-diastolic pressure. The author has used opiates during cardiopulmonary bypass when the heart is not involved in the circulation and still observed a fall in systemic arterial pressure. It would seem therefore that, in intact man, direct myocardial depression is not the cause of hypotension following opiates.

In comparing morphine with heroin we chose dose levels which are generally accepted as equi-analgesic (Foldes, Swerdlow and Siker 1964) although some workers (Reichle, Smith, Gravenstein, Macris and Beecher 1962) have suggested that heroin's potency may be more than twice as great as morphine. Dundee, Loan and Clarke (1966) found that increasing the dose of morphine from 10 to 15 mg had a negligible effect on its soporific action, whereas increasing the dosage of heroin from 5 to 7.5 mg significantly increased the degree of drowsiness. These findings could suggest that heroin

may be more than twice as potent as morphine. However, the differing time course of action of the 2 drugs may account for minor differences found by these workers.

In this study morphine produced a small initial rise in cardiac output and heart rate, changes which were not observed in patients who received heroin. There was no difference in the other circulatory effects of these 2 drugs and in particular neither produced a dramatic fall in arterial pressure. Although the circulatory effects of morphine were slightly greater than those of heroin, in terms of practical therapeutics, the advantages of heroin over morphine seem small. However, the patient numbers in this series were small due to the detailed nature of the study and might not be representative. It seemed essential to carry out a more definitive study on a larger number of patients paying particular attention to the changes in blood pressure and heart rate.

A 'BLIND' TRIAL OF THE EFFECTS OF MORPHINE AND HEROIN IN ACUTE MYOCARDIAL INFARCTION

CHAPTER VI

'BLIND' TRIAL OF CIRCULATORY AND RESPIRATORY EFFECTS OF MORPHINE AND HEROIN

Methods

In this study the patients were allocated on a randomized basis to drug therapy with either morphine or heroin. Twenty-seven patients were studied; they had sustained a recent myocardial infarction as judged by World Health Organisation (1959) criteria within the previous 36 hours. No patient was shocked or had marked lung crepitations, they were all in sinus rhythm and no patient had prior drug therapy within 12 hours preceding the study. All the patients were informed of the nature of the study and their permission to undertake the study was obtained. It was explicitly stated that this investigation was not part of their standard treatment.

Prepared numbered ampoules containing either morphine 10 mg or heroin 5 mg were kept under refrigeration to maintain the purity of the heroin. No one involved in the clinical treatment of the patient nor in the preliminary evaluation of the results knew to which therapeutic group the patients had been allocated.

The patients were studied in their own beds in the clinical

investigation and therapy area. The study was conducted in the supine position, the head being supported by one pillow. Routine patient monitoring was continued, the E.C.G. being used to count the heart rate. A small polyethylene catheter was inserted into the brachial artery under local anaesthesia. Arterial pressure was measured using a Statham strain gauge manometer (P23 Db) and recorded on standard recording equipment. Pressure recording was continued throughout the study apart from intervals for the sampling of arterial blood. A small indwelling needle was placed in a peripheral vein to enable the injection of the analgesic without disturbing the patient. After the insertion of the catheters, the patient was allowed to settle for a period of at least 30 minutes before the study commenced. During the study, arterial blood was sampled 3 times during the control period and at 10, 20, 30 and 45 minutes after the start of the injection. The samples were analysed for oxygen and carbon dioxide tension and pH. Throughout the study the patient was clinically assessed for drowsiness, sleepiness, sweating, nausea and vomiting and these clinical features were recorded on the patient's proforma sheet at 5 minute intervals.

Statistical Methods: Biological data is often difficult to interpret because of difficulty in achieving satisfactory control periods. Even in the most stable periods, most biological variables have cycling time courses. In an attempt to avoid difficulties in time-series statistics, a variable control period ranging from 15 to 25 minutes

was selected. The precise selection was made on a randomized basis. Thus one element of the statistical analysis is the time interval between the time of occurrence of an effect, hypothetically due to the drug and the (randomly chosen) time of injection of the drug. The point of this was to ensure valid statistical confirmation that observed changes were true effects of the drug and not due to artefact or to physiological changes independent of the drug.

Statistical analysis of heart rate and blood pressure was first made by replotting the individual patient data on a modified cumulative total graph. This integrative process is a sensative method of detecting small, moderately persistent changes of level of the variable being studied (Healey 1968). The precise slope of the cumulative plot is unimportant. What is important is a sharp change in angle indicating a change in the variable being examined. A sharp increase (or decrease) in the angle of slope on the cumulative plot indicates a corresponding increase (or decrease) in the prevailing level of blood pressure or heart rate.

An example of cumulative plot (cusum) for an individual patient is shown in fig. 33. Changes in mean arterial blood pressure are plotted in absolute values and as a cumulative plot. Six minutes after the start of the administration of the opiate the cusum plot showed a change in angle of approximately 90^{o}. This indicates a change in the variable being observed. From the cusum plots of each patient, the total number of increases or decreases in heart

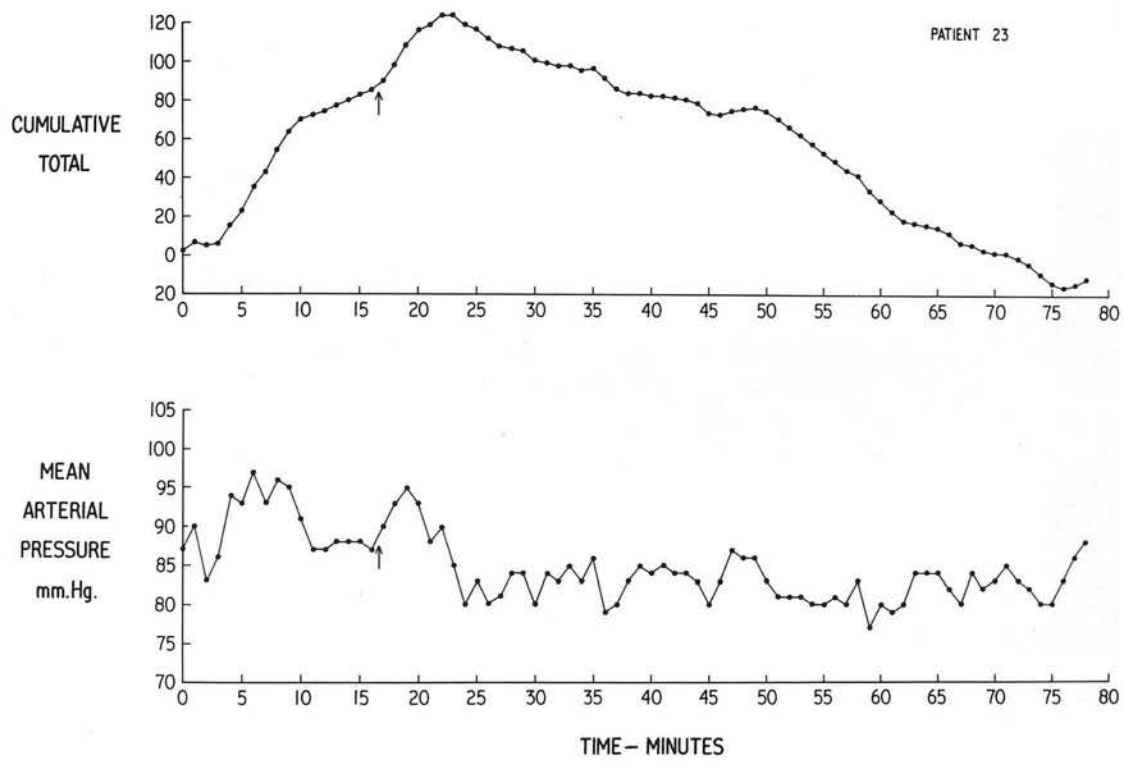


Fig. 33

Changes in mean arterial pressure in one patient before and after the administration of an opiate. Blood pressure is plotted in absolute value and as a cumulative plot (cusum). There is a marked change in the slope of the cusum plot 6 minutes after the start of the injection of the opiate.

rate and blood pressure were noted. Subsequently standard statistical tests were applied.

RESULTS

Clinical Effects (fig. 34)

Of the 27 patients, 14 patients received morphine and 13 patients received heroin. One patient felt nauseated during the study and vomited 20 minutes after administration of the drug. In this case the drug administered was heroin. Sweating was more commonly observed with heroin than morphine but this difference was not statistically significant. Similarly there was no statistical difference between the 2 drugs in relation to the drowsiness and sleepiness produced. It was sometimes difficult to determine whether the patients were truly sleeping or only drowsy, but whether these 2 effects were assessed separately or together, there was no significant difference between the 2 groups when examined by the 'Chi Square' test. There were however, 5 patients who complained of a feeling of 'light headedness' 5 minutes after the administration of heroin. Only one patient felt 'light headed' after the administration of morphine.

Mean Arterial Pressure: Each trace was analysed by the cusum plot, if the plot showed a change in slope of greater than 30^{o} after the drug had been administered, it was taken as indicating a positive drug effect. As judged on positive reactions on the cusum plots 8 of the 13 patients who received heroin and 9 of the 14 patients who received morphine had a fall in blood pressure following the

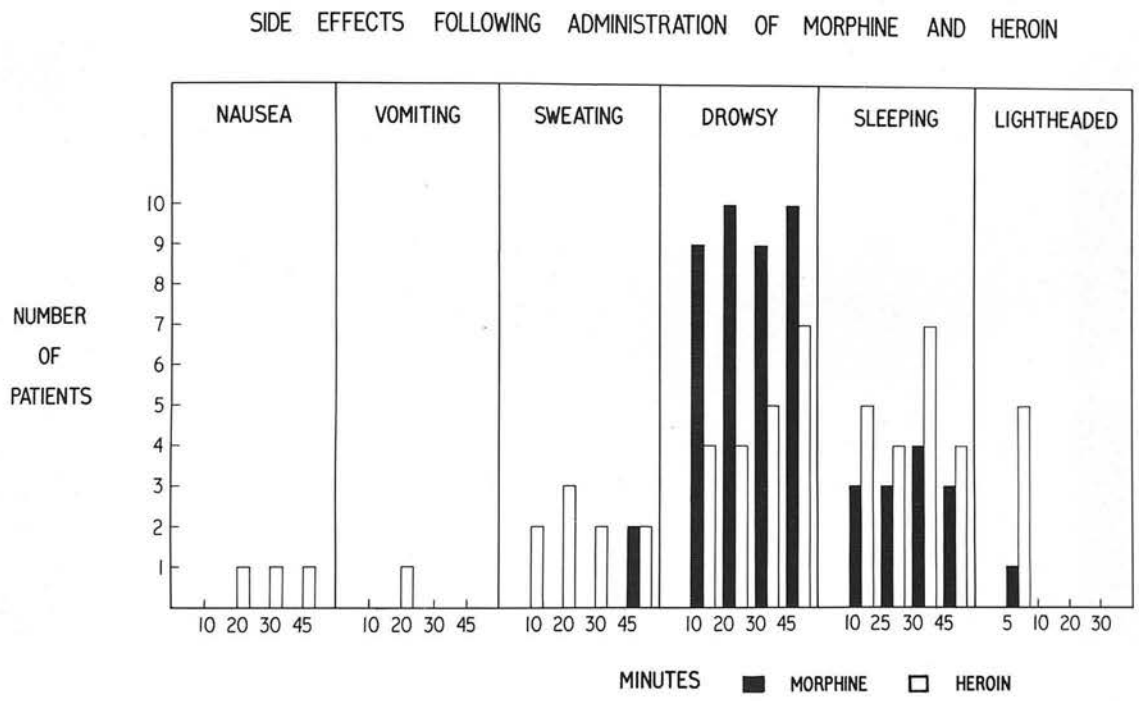


Fig. 34

The clinical effects of morphine and heroin administered on a 'blind' basis. (Morphine n = 14; heroin n = 13).

administration of the opiate. A fall in mean arterial pressure greater than 15 mm Hg occurred in 2 patients who had heroin (-19 and -21 mm Hg) and in 3 patients who had morphine (-17, -20 and -23 mm Hg).

The results were also analysed in standard statistical manner. The mean changes following therapy with morphine or heroin are shown in fig. 35. Both drugs produced a fall in blood pressure, the fall occurring within 10 minutes. At this time the mean reduction in blood pressure was 8 mm Hg in the morphine treated group and 5 mm Hg in the heroin treated group. These changes are small and neither they nor their differences are statistically significant. (Table 13).

When the patients were sat up at the end of the study, changes in blood pressure were small and variable. In a number of patients, there was slight rise in systolic blood pressure when sat erect. In no patient did severe postural hypotension occur (fig. 36).

Heart Rate: There was no significant difference in the number of changes in angle of cusum plots after morphine or heroin. Both drugs produced a slight increase in heart rate at approximately 10 minutes after the start of the injection. The changes were small, averaging some 2% increase. The mean changes for both groups are shown in fig. 37. The greatest individual increase, following morphine, was 12 beats per min and 14 beats per min following heroin. There was no patient who showed marked bradycardia, the greatest individual decrease in heart rate (7 beats per min) followed the administration of heroin (Table 14).

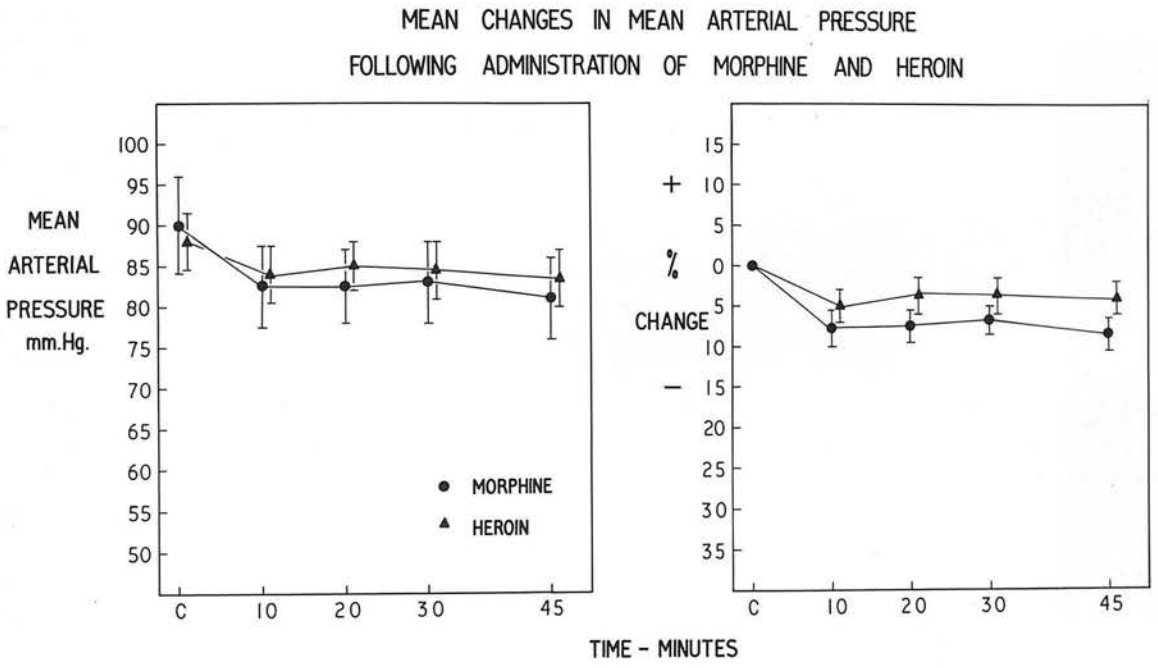


Fig. 35

Changes in mean arterial pressure following morphine and heroin administered on a 'blind' basis. (Morphine n = 14; heroin n = 13).

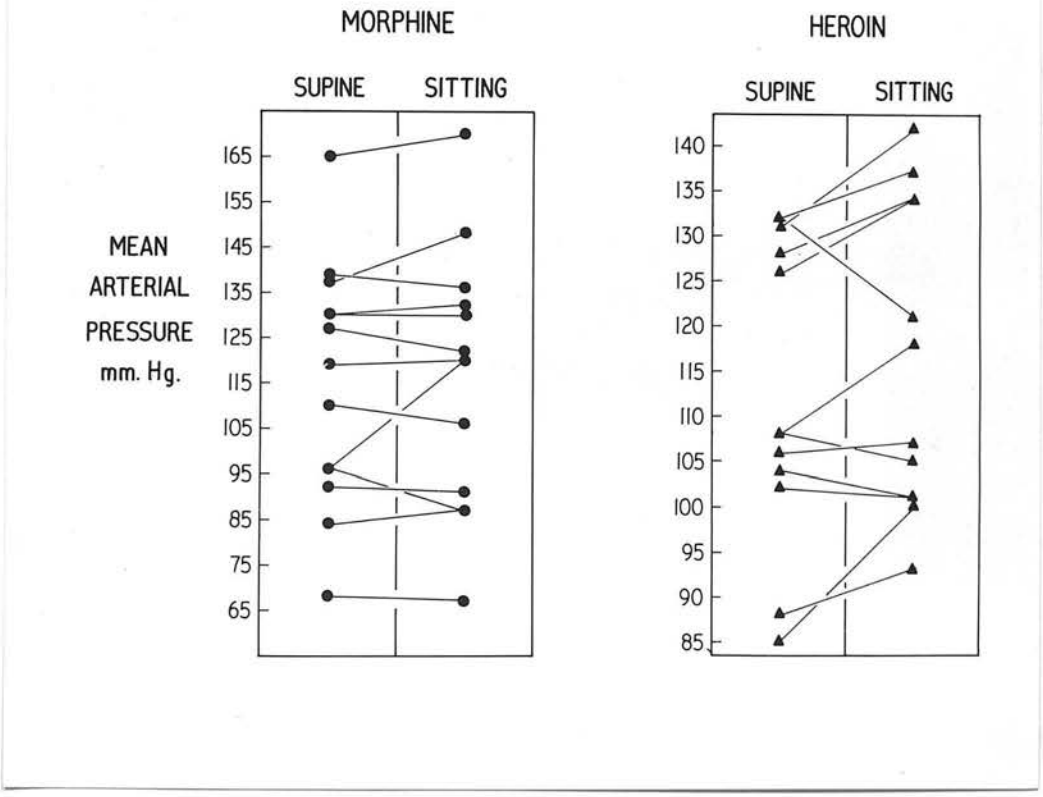


Fig. 36

Alterations in mean arterial pressure after changing from the supine to sitting position after therapy with opiates.

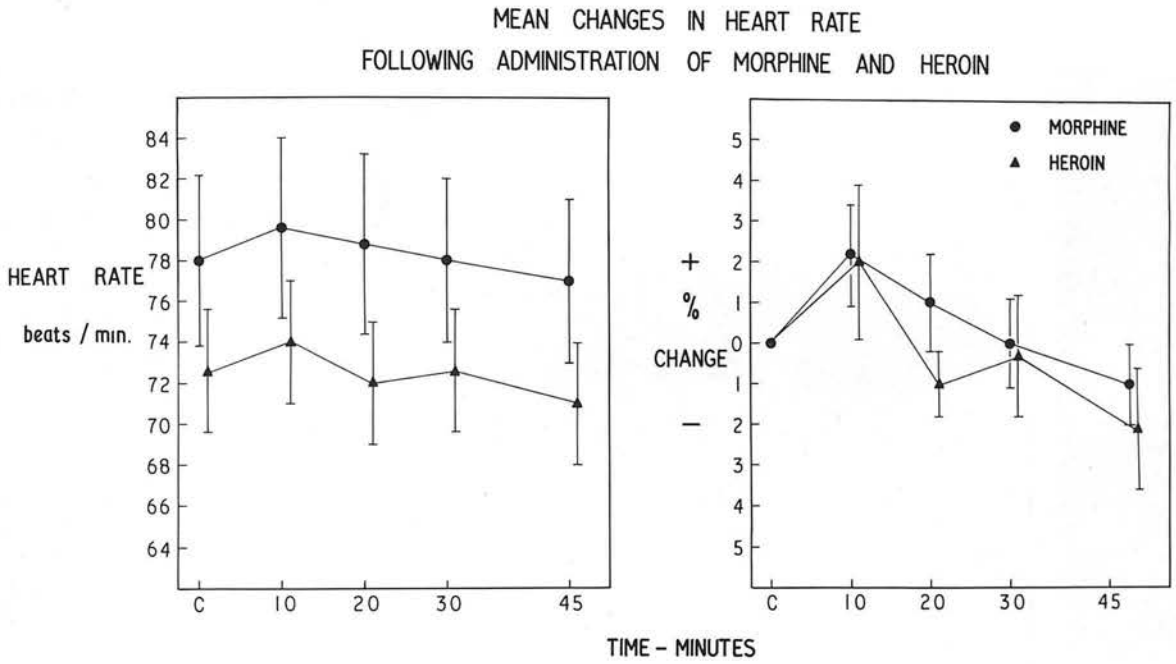


Fig. 37

Changes in heart rate following the administration of morphine and heroin. (Morphine n = 14; heroin n = 13).

Arterial Oxygen Tension: The initial arterial oxygen tensions (PaO_2) were reduced in all patients, ranging from 43 to 70 mm Hg whilst breathing air. The heroin treated group had a lower PaO_2 in the control period, but this was probably fortuitous as the groups were randomly selected. The administration of opiate brought about a further decrease in PaO_2 (fig. 38). The reduction in PaO_2 was most marked 10 minutes after the administration of heroin, the mean PaO_2 for the group being reduced by 8 mm Hg. This reduction was most marked at 10 minutes and by 30 minutes the level was back to that of the control period, The reduction in PaO_2 following morphine was significantly less than with heroin ($p < 0.02$) (Table 15).

Arterial Carbon Dioxide Tension: The mean arterial carbon dioxide ($PaCO_2$) prior to the administration of opiates was 40 mm Hg. Ten minutes following morphine the mean for the group was increased by 3 mm Hg and following heroin by 5 mm Hg (fig. 39). There was thus a slightly greater increase in $PaCO_2$ following heroin than morphine but the changes for the groups were not significantly different (Table 16).

Arterial Hydrogen ion Concentration: Hydrogen ion concentration ($/\bar{}H^+_{\bar{}}/$) were derived from the measured pH. Both groups had a mean $/\bar{}H^+_{\bar{}}/$ 36 nm/litre prior to the administration of opiates. The $/\bar{}H^+_{\bar{}}/$ in both groups increased after the administration of heroin and morphine. There was a greater increase in $/\bar{}H^+_{\bar{}}/$ 10 minutes after the administration of heroin and when plotted in percentage

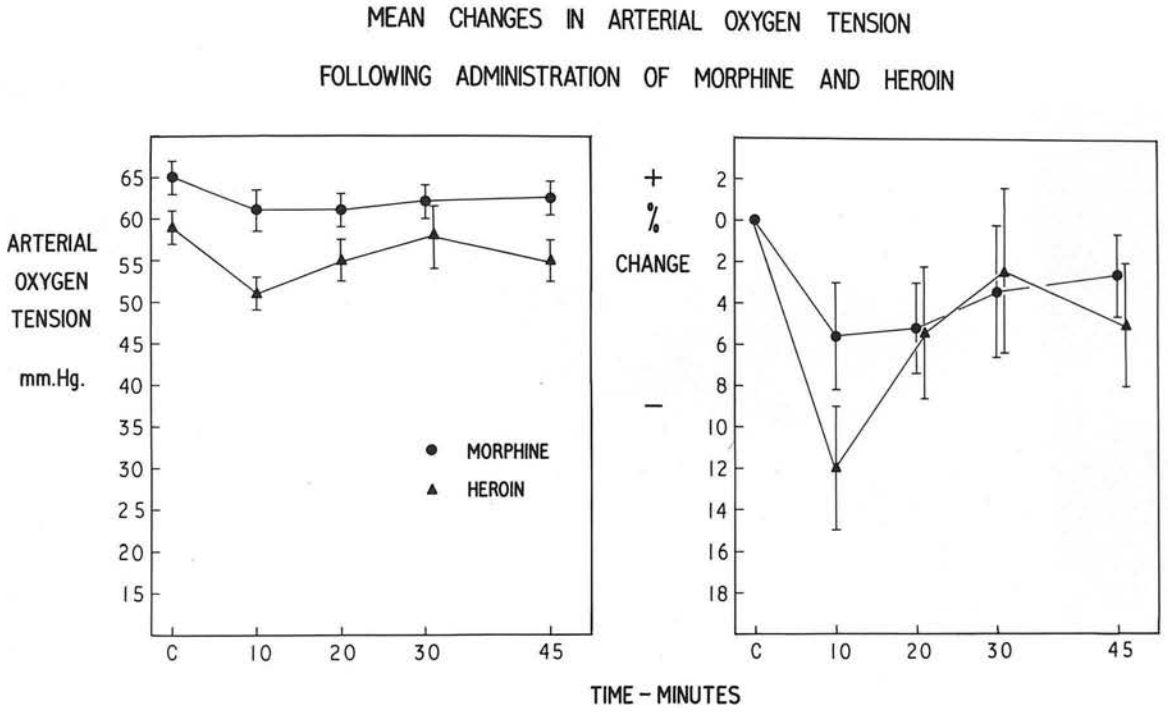


Fig. 38

Changes in arterial oxygen tension following the administration of morphine and heroin. (Morphine n = 14; heroin n = 13).

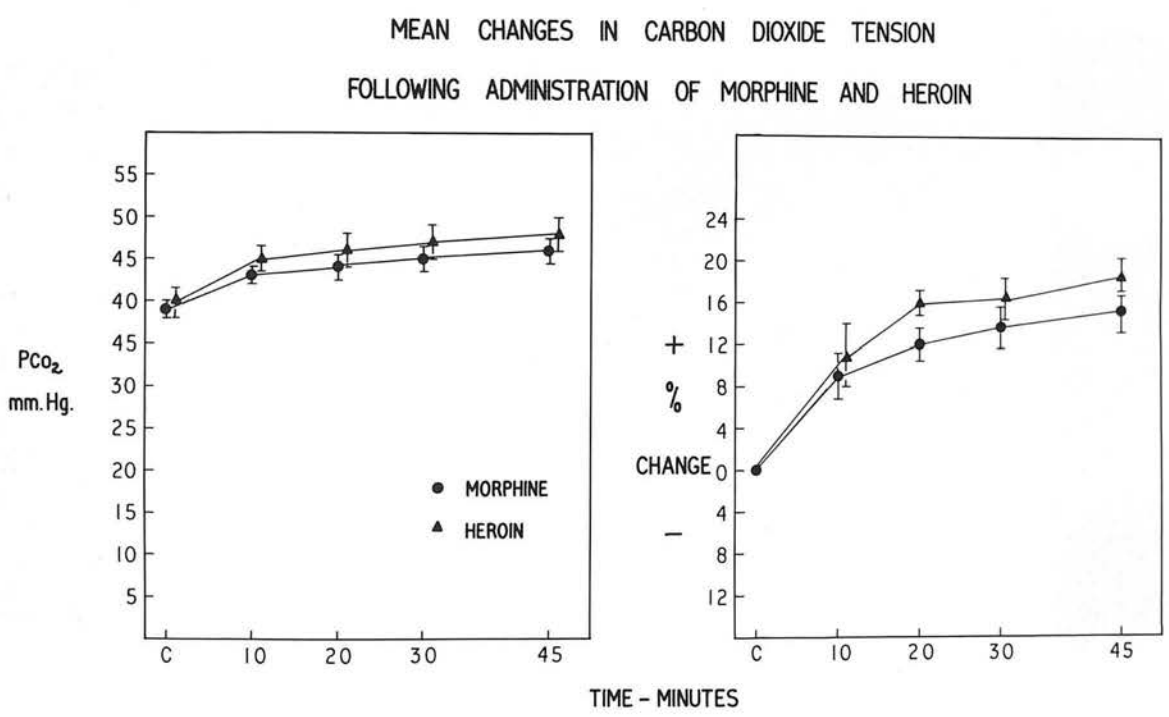


Fig. 39

Changes in arterial carbon dioxide tension following the administration of morphine and heroin. (Morphine n = 14; heroin n = 13).

fashion this increase echieves statistical significance at the 5% level (fig. 40) (Table 17). The measured values of pH are shown in Table 18.

Inter-relationship of Data: Dose response curves were constructed for the morphine and heroin groups. Within the small range of variation in dosage, changes in blood pressure were not related (morphine r = 0.163, heroin r = 0.172) to the dose in mg per kilogram for either group.

Similarly changes in blood pressure show a low correlation with changes in arterial carbon dioxide tension (morphine r = 0.347, heroin r = 0.013).

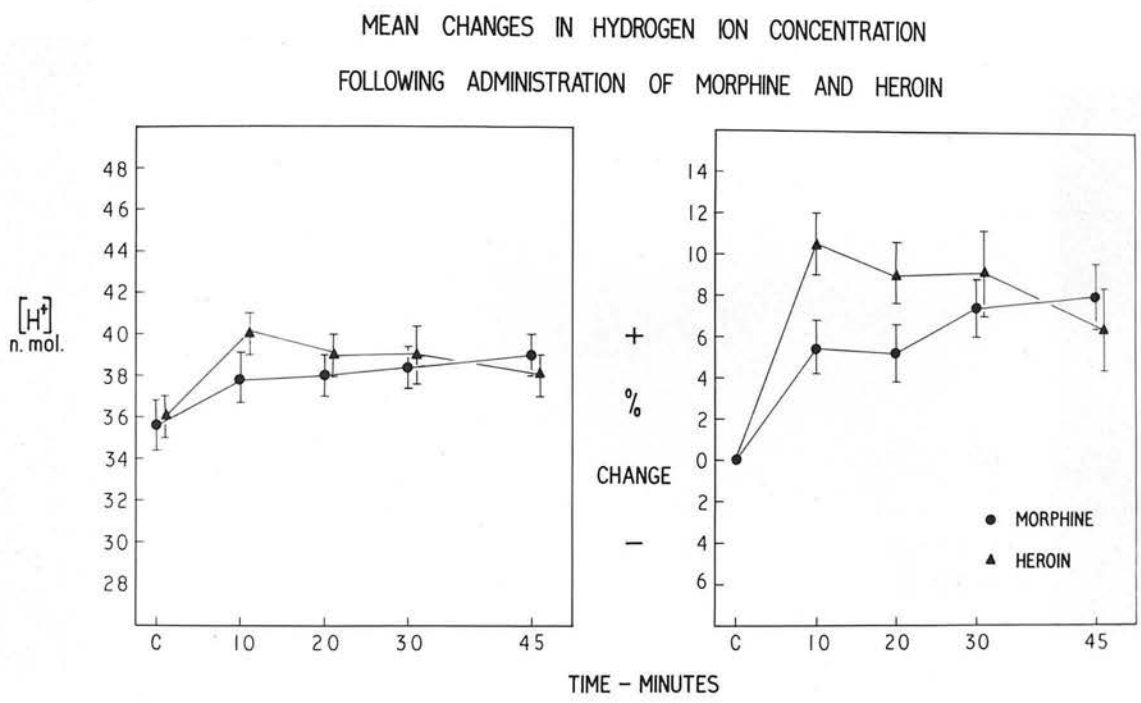


Fig. 40

Changes in arterial hydrogen ion concentration following the administration of morphine and heroin. (Morphine n = 14; heroin n = 13).

DISCUSSION

The present study confirms that there are variable but relatively minor circulatory effects following the administration of morphine or heroin to patients with acute myocardial infarction. These findings are the same as those demonstrated in the previous chapter and are similar to the findings of Thomas and colleagues (1965). However, in no patient in the present study was there a profound fall in blood pressure.

The report of hypotension following morphine by Thomas and his colleagues was influenced by the marked hypotension occurring in a single patient and in this patient the hypotension was in association with marked bradycardia. Although they did not publish detailed tables, nor undertake any statistical analysis by using the data derived from their published diagrams, a statistical analysis using a paired 't' test did not reveal a significant fall in blood pressure after morphine.

No marked postural changes in blood pressure occurred when the patients were sat up at the end of the study, the commonest response being a slight increase in systolic blood pressure. Eddy and Singh (1969) examined the effect of nursing posture in 9 patient after acute myocardial infarction. On sitting upright, systolic blood pressure increased in 3 patients (2-12 mm Hg) and decreased in the remaining 6 patients (5-20 mm Hg). In the current study the

administration of opiates did not impair normal circulatory responses. However, none of the patients had their legs dependent whilst sitting up; postural hypotension can occur in normal subjects when sat upright with legs dependent (Sapru 1966).

Changes in heart rate were small, both drugs producing a slight increase in heart rate. In particular in no patient was there a significant bradycardia. In the report by Thomas and his colleagues it is difficult to be certain whether the bradycardia in the patient with marked hypotension was caused by morphine or by some independent physiological mechanism, such as a vasovagal attack.

Animals and particularly dogs, develop bradycardia after the injection of morphine (Kreuger, Eddy and Sumwalt 1941). The effects on man are more variable. Papper and Bradley (1942) did not observe any change in heart rate after the intravenous injection of 10 mg of morphine to 6 normal subjects. Denton and Beecher (1949) found statistically significant slowing of the pulse rate on 29 subjects given either morphine or 3 methadone derivatives. Drew, Dripps and Comroe (1946) observed an increase in heart rate after morphine (10-30 mg) when given intravenously, but when given intramuscularly, there was no significant change in heart rate. The bradycardia in animals is believed to be a central effect mainly by an action on the vagus centre. The excitability of the vagus nerve is increased after morphine, but Allen, Murphy and Meek (1945) showed that morphine does not produce bradycardia in decerebrate dogs. Reynolds

and Randall (1957) concluded that morphine bradycardia in dogs was due to the blocking of cortical impulses which normally exert an inhibiting influence on medullary vagal tone. The cardiac slowing and arrhythmia observed in normal dogs produced sino-atrial and atrio-ventricular heart block (Eyster and Meek 1912). This depression of normal conductivity could be reversed by atropine but the effects of atropine passed off more quickly than that of morphine.

If bradycardia were a regular feature in man its occurrence could be prevented by atropinization. However, the analgesic action of the opiate might then be reduced (Gross, Holland, Carter and Christensen 1948). The absence of bradycardia in these studies involving a total of 25 patients who received morphine and 23 patients who received heroin suggests that routine atropinization is unnecessary and indeed probably undesirable.

Opiates usually cause reduced ventilation and cause an increase in arterial P_{CO_2}. The increase parallels the degree of respiratory depression. Loeschke, Sweel, Kough and Lambertson (1953) noted a mean rise of alveolar P_{CO_2} of 2.6 mm Hg following 10 mg of morphine to 6 normal subjects. Habib (1966) administered morphine in varying doses to 13 normal subjects and produced a mean increase in arterial P_{CO_2} of 2.76 mm Hg. In this study the administration of morphine caused an increase of 5.4 mm Hg in arterial carbon dioxide tension: heroin caused an increase of 6.3 mm Hg in arterial carbon dioxide tension. The increase in carbon dioxide tension occurred more

quickly in the patients who received heroin than in those who had morphine.

There was a similar early increase in hydrogen ion concentration in those patients who had heroin. This increase was significantly greater 10 minutes after drug administration in the patients treated with heroin than with those treated with morphine. This suggests an earlier onset of action of heroin and is in keeping with the observations of Way, Kemp, Young and Grassetti (1960). They showed that heroin was rapidly broken to 6 mono-acetyl morphine and that this substance was rapidly transferred across the blood brain barrier. Morphine is transferred more slowly to brain tissue.

As noted by MacKenzie and colleagues in 1964 and also demonstrated in Chapter III, low arterial oxygen tensions occur even in "uncomplicated" myocardial infarction. The patients in this study all had reduced arterial oxygen tensions and this was reduced further after the administration of opiates. This was particularly marked after treatment with heroin. The earlier action of heroin may be of advantage in the relief of pain but the greater reduction in arterial oxygen tension suggests that it is best used when the patient is also receiving oxygen.

The increase in carbon dioxide tension might be expected to influence the degree of hypotension following opiates. Both an increased cardon dioxide tension and an increased hydrogen ion concentration cause vasodilatation of cutaneous, skeletal muscle,

renal and cerebral vascular beds (Shepherd 1963). In the present study no correlation could be found between changes in $PaCO_2$ or $/\bar{}H^+\bar{}/$ and the degree of hypotension. Moreover, the respiratory changes occurred later than the fall in blood pressure.

Conclusion

These studies have failed to show a great difference between the circulatory effects of morphine and heroin, both drugs producing some degree of hypotension, but not marked and not sufficient to cause circulatory impairment. The respiratory effects of heroin were more marked than those of morphine. It is disappointing that the findings do not consistently demonstrate any clear cut advantages of one drug over the other. The earlier action of heroin may be of advantage in relief of pain, but the greater depression of arterial oxygen tension following its use suggests that it is best used when the patient is also receiving oxygen. Increasing the number of patients might have produced a statistically significant result but Atkins (1966) has emphasised that a result obtained in this manner is unlikely to be of clinical importance. Lasagna in 1964 examined the addictive properties, analgesic action and side effects of the 2 drugs and concluded that there was little difference between morphine and heroin. A similar conclusion was reached by Dundee, Clarke and Loan (1967) in a study of the side effects of the 2 drugs. The evidence presented here suggests that there is little difference in the circulatory effects of the 2 drugs. Were the future supplies of heroin to be threatened, the published evidence

suggests that the more traditional and standard morphine is a suitable opiate for use in acute myocardial infarction. In terms of practical therapeutics these studies have demonstrated no important difference between the 2 drugs.

CONCLUSIONS AND RECOMMENDATIONS

Cardio-respiratory Findings:

These investigations have shown that nearly all patients with recent myocardial infarction have abnormal cardio-respiratory function. The more severely ill the patient, the greater is the degree of cardiac failure and respiratory abnormality. Even in patients with so called 'uncomplicated' myocardial infarction, cardiac output is in the low normal range and the mixed venous oxygen saturation is decreased. A number of these patients have raised pulmonary arterial pressures and most have arterial hypoxia with abnormal ventilation perfusion ratios. The mismatching of ventilation and perfusion probably results from raised pulmonary venous pressures and decreased perfusion to the lung base. The clinical diagnosis of left ventricular failure is not always easy and the abnormal cardio-respiratory function suggests that sub-clinical left ventricular failure is a relatively common finding in acute myocardial infarction.

The similarity of the abnormal circulatory and pulmonary function in patients with clinical left ventricular failure and those with shock suggests that severe left ventricular failure is present in both groups. The high pulmonary artery pressures recorded in cardiogenic shock are in accord with this view. Patients with left ventricular failure and cardiogenic shock have severe hypoxaemia and the more severely ill the patient, the greater the degree of

veno-arterial shunting. This shunting is probably a reflection of non-functioning gas exchanging units filled with oedema fluid or collapse due to peribronchial cuffing or to loss of alveolar surfactant.

In cardiogenic shock the very low cardiac output leads to impaired tissue perfusion and to metabolic acidosis. Abnormal regional perfusion to areas such as the splanchnic bed may increase lactic acidosis because of impaired liver function. The hypoxaemia and metabolic acidosis may in turn cause a decrease in myocardial contractility leading to a further decrease in cardiac output.

The finding of a mixed metabolic and respiratory acidosis in some patients with failure and shock is worth stressing. This condition can only be detected by blood gas analysis and early detection and prompt therapy by assisted ventilation can be life saving (Anthonisen and Smith 1965, Avery, Samet and Sackner 1970).

The haemodynamic findings in the patients with cardiogenic shock are in close agreement with most published series (Freis et al. 1952, Smith, Wikler and Foz 1954, Lee 1957, MacKenzie et al. 1964, Gunnar et al. 1966, Smith et al. 1967). The report by Shubin et al.(1968) is of note for, in developing their prognostic index, they divided their patients with cardiogenic shock into two groups, the survivors and the non-survivors (Table 2). The haemodynamic findings in the survivors fit within the standard deviations of the circulatory measurements for group I - the uncomplicated group. The

haemodynamic findings in the non-survivors is similar to the findings for the Group III patients, those with cardiogenic shock. Any report of successful therapy in cardiogenic shock must be related to the initial haemodynamic status of the patients.

Simple Monitoring Procedures:

In many hospitals a detailed haemodynamic study may be impossible. What are the simpler variables that can be recorded to provide objective evidence of the patients' initial haemodynamic status? Blood gas analysis will provide evidence of the patients' acid-base status. In cardiogenic shock some measurement of systemic blood pressure is required and in most patients this can only be assessed with any degree of confidence by arterial cannulation and measurement by a pressure transducer. Urine flow will provide some index of renal function and this certainly warrants urethral catheterisation. The close relationship of mixed venous oxygen to cardiac output demonstrated in Chapter III can be used to assess total blood flow. Mixed venous oxygen saturation is easily obtained by a 'float-in' technique and moreover as pressure measurements are also obtained, left heart filling pressures can be assessed.

Therapy for Shock and for Severe Left Ventricular Failure Complicating Acute Myocardial Infarction:

1. Relief of Pain: The studies presented in Chapters V and VI show that recent reports of the hazards of morphine have been exaggerated

and that there is little practical difference between morphine and heroin. At present morphine is probably a satisfactory analgesic for the relief of pain in acute myocardial infarction.

2. Administration of Oxygen: In patients with left ventricular failure and shock, hypoxaemia is likely to be present. Whilst a normal physiological response to breathing high concentrations of oxygen is unlikely, in nearly all patients there will be an increase in arterial oxygen tension. In most patients this will produce almost complete oxygen saturation of the arterial blood. As yet there is little information on the amount of hypoxia compatible with life. Flenley (1967) suggested that therapy should aim to provide a partial pressure of oxygen of at least 10 mm Hg at the cellular mitochondria. Other workers have suggested that the cellular mitochondria operate at oxygen partial pressures of 1 mm Hg (Dickens and Neil 1964). It is difficult to confirm or refute this, as measurements of mixed venous oxygen tension do not indicate the adequacy of oxygen delivery to any one tissue area. Even measurement of oxygen tension in effluent blood from one organ does not indicate the adequacy of tissue oxygenation, as shunting in the micro-circulation can occur. In patients with cardiogenic shock, poor tissue perfusion is probably more important than arterial hypoxia in inadequate tissue oxygenation. Nevertheless, arterial hypoxia is marked and this hypoxia can be partially corrected with comparative ease.

There is a small increase in systemic arterial pressure when oxygen is breathed (MacKenzie et al. 1964, Cameron et al. 1966, Foster et al. 1969) and cardiac output is little changed. Calculated systemic vascular resistance is increased and therefore the work load of the heart is increased (Foster et al. 1969).

However this small increase in work load could easily be offset by other potential benefits such as a greater oxygen tension in ischaemic myocardium around the infarcted area. As yet there is no statistical proof of the benefits of oxygen therapy in myocardial infarction and its true value remains somewhat speculative, but for the present oxygen tensions are best measured and hypoxia corrected.

Specific Therapy: It would seem dangerous to attempt to generalise in recommending any specific therapy for the treatment of cardiogenic shock. Ideally these patients should be managed in a special treatment area with facilities for measuring all aspects of circulatory function and therapy directed to specific abnormalities. On the basis of the findings presented in Chapter III, inotropic agents such as digitalis seem logical, but the poor response to digoxin documented in Chapter IV and also noted by MacKenzie (1965), by Cohn, Tristani and Khatri (1969) and by Gunnar et al. (1970) suggest that a successful response is unlikely. Perhaps the philosophy of therapy in cardiogenic shock should be to regard these patients as on a knife edge. Various therapeutic manoeuvres may possibly improve cardiac output and lead to improved tissue perfusion

with a decrease in metabolic acidosis and an increase in myocardial contractility. For this reason, acid-base correction should be attempted and an inotropic agent such as digoxin tried. Recently there has been increased interest in the inotropic activity of glucagon and Puri and Bing (1969) suggested its use in cardiogenic shock. Certainly any drug that can increase cardiac output in cardiogenic shock will be of value.

However, the failure of many pharmacological agents to help patients in cardiogenic shock has led to investigations of various mechanical assistance techniques (Kantrowitz, Krakauer, Butner, Freed, Jaron, Rosenbaum, Goodman, 1969). There are many problems in design, engineering and physiology of assisted circulation and a number of ingenious solutions have been devised. However, even when total blood flow during assisted circulation seems adequate, abnormal regional perfusion may persist, (Muir and Davidson, 1970).

Although pathological studies have shown that in general cardiogenic shock and severe failure are associated with extensive infarction, we have no knowledge of the size of the infarcted area at the time of onset of cardiogenic shock. If the infarcted area was always large then a nihilistic view of future progress in the management of cardiogenic shock would be tenable. If on the other hand the infarcted area were relatively small, and the low output state caused the area to extend, than a much more aggressive policy regarding assisted circulation and even surgery would be warranted.

Possible approaches to the problem of initial ventricular damage include angiographic studies and the labelling of viable myocardium by isotope or tetracycline shortly after the onset of shock. Certainly any prospect of lessening the mortality in this common condition will be most welcome.

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TABLE 1

	MEAN ARTERIAL PRESSURE (mm.Hg)	CARDIAC INDEX ($l.min.m^{2}$)	STROKE VOLUME (mls.)	SYSTEMIC VASCULAR RESISTANCE (dynes.sec. $cm.^{-5}$)	VENOUS PRESSURE (mm.Hg)	n	COMMENTS
FREIS et al. (1952)	I 95 ± 11	3.4 ± 0.8	76 ± 14	1175 ± 100	6.5	4	Dye dilution (Evans blue). Central injection.
	II 89 ± 20	2.9 ± 0.3	50 ± 9	1325 ± 250	8.5	5	
	III 79 ± 11	1.8 ± 0.4	27 ± 7	2050 ± 450	8	4	
SMITH et al. (1954)	I 86	2.4	-	1760	6.1	9	Dye dilution.
	II -	-	-	-	-	-	Peripheral injection.
	III 70	1.6	-	1840	9.9	7	Arterial sampling.
GILBERT et al. (1954)	I 100	2.6	-	1679	9.6	7	Evans blue peripheral injection.
	II 100	1.9	-	2300	12.3	6	
	III 73	1.0	-	2950	15.8	7	Arterial sampling.
GAMMIL et al. (1955)	I -	4.3	104	1272	7.3	11	Evans blue peripheral injection.
	II -	3.0	60	1668	8.4	24	Arterial sampling.
	III -	-	33	1900	-	2	B.P. by sphygmomanometer.
LEE (1957)	I 93	4.4	81	942	-	4	
	II 100	3.2	74	1426	-	5	
	III 99	3.0	64	1483	-	2	
BROCK et al. (1959)	I -	3.0	70	-	-	18	Peripheral injection. Earpiece sampling.
	II -	2.0	43	-	-	17	
	III -	-	-	-	-	-	All patients on oxygen.

	MEAN ARTERIAL PRESSURE (mm Hg)	CARDIAC INDEX (l min m^2)	HEART RATE (beats min)	STROKE VOLUME (ml m^2)	SYSTEMIC VASCULAR RESISTANCE (dynes sec cm^{-5} m^2)	CENTRAL VENOUS PRESSURE (mm Hg)	REMARKS
Gunnar et al. (1966)	I 92 ± 23	*		*	**	-	* not indexed for body surface area. ** mm Hg l min No zero level.
		3.8 ± 1.5	-	43 ± 18	26 ± 9		
	III 53 ± 12	2.2 ± 0.9		21.5 ± 6	27 ± 23	7.9 ± 6.8	
Smith et al. (1967)	I -	-	-	-	-	-	Zero level 5 cms below sternal angle.
	III 63 ± 13	1.6 ± 0.5	98 ± 25	17 ± 5	2824 ± 1000	9.2 ± 4.2	
SHUBIN et al. (1968)	IIIa 76 ± 6	2.8 ± 0.9	82 ± 20	35 ± 12	1250 ± 625	7.7 ± 5	IIIa represents group who survived. No zero level.
	IIIb 54 ± 17	1.3 ± 0.6	87 ± 28	15 ± 8	1855 ± 1027	11.2 ± 4.1	

TABLE 2

UNCOMPLICATED MYOCARDIAL INFARCTION

	SEX	AGE	HT.	WT.	S.A.	PAIN	DYSPNOEA	JVP	LUNG CREPITATIONS	E.C.G.	SERUM ENZYMES		CHEST X-RAY
											SGOT	SCPK	
AD	M	54	173	76	1.90	0	0	0	0	Ant. transmural	52	-	clear
McW	M	63	162	60	1.62	⊖	0	0	0	Ant. lat. intramural	78	-	clear
LE	M	59	174	76	1.90	0	0	0	0	Inf. intramural	53	-	clear
SH	M	46	171	80	1.91	+	0	0	0	Inf. intramural	52	420	clear
McH	M	41	173	72	1.86	0	0	0	0	Ant. lat. transmural	102	-	clear
CR	M	71	176	54	1.65	0	0	0	Few at bases	Ant. transmural	84	-	clear
RI	M	56	175	78	1.92	0	0	0	0	Inf. transmural	56	-	clear
DA	M	48	168	76	1.86	0	0	+	0	High lat. transmural	58	-	clear
WH	M	59	182	93	2.12	0	0	0	Few at bases	Ant. transmural	98	120	? Pulmonary oedema
AR	M	53	168	78	1.88	0	0	0	0	Inf. transmural	62	-	clear
McL	M	77	178	70	1.86	0	0	0	Few at bases	Inf. transmural	66	220	Pulmonary vascular congestion
TH	F	43	153	81	1.79	0	0	0	0	Ant. lat. transmural	98	-	clear
ST	M	62	165	66	1.71	0	0	0	0	Inf. transmural	76	-	clear
DI	M	52	173	67	1.79	0	0	+	Few at bases	Ant. lat. transmural	100	-	Pulmonary vascular congestion
DO	F	55	158	72	1.72	+	0	0	0	Ant. transmural	72	-	clear
SC	F	64	170	70	1.81	0	0	0	0	Ant. transmural	80	-	clear
MU	M	56	183	75	1.98	0	0	0	Few at bases	Inf. transmural	240	1800	Pulmonary vascular congestion
AL	M	64	164	68	1.73	0	0	0	0	Inf. transmural	98	-	Some congestion of lung fields
HE	M	60	168	76	1.86	0	0	+	Few at bases	Inf. transmural	58	-	Congestion of lung fields
RO	M	59	163	64	1.68	0	0	+	0	Ant. lat. transmural	64	520	Pulmonary vascular congestion
FR	M	42	168	65	1.73	0	0	0	0	Ant. intramural	53	-	clear
SO	M	61	169	68	1.80	0	0	0	0	Ant. transmural	100	-	clear
THO	M	64	163	70	1.75	0	0	0	0	Inf. transmural	66	-	clear
PE	M	58	167	67	1.75	0	0	0	0	Ant. transmural	78	-	clear
THN	M	66	163	72	1.73	+	0	0	0	Inf. and Lat. transmural	53	-	clear
FL	M	67	176	72	1.87	0	0	0	0	Ant. transmural	75	-	clear

TABLE 4

LEFT VENTRICULAR FAILURE COMPLICATING ACUTE MYOCARDIAL INFARCTION

	SEX	AGE	HT.	WT.	S.A.	PAIN	DYSPNOEA	JVP	LUNG CREPITATIONS	E.C.G.	SERUM ENZYMES		CHEST X-RAY	COMMENTS
											SGOT	SCPK		
CO	M	64	162	52	1.53	0	+	+	Both bases	Ant. transmural	90	-	Increased veins in upper lobes	
HO	M	52	165	66	1.72	0	+	++	Both bases	Post transmural 1^{o} heart block	54	440	Congestion of lung fields	Persistent failure for many weeks
SL	F	41	160	67	1.69	0	++	++	Throughout lung fields	Ant. transmural frequent V.E.S.	86	-	Congestion of lung fields	Persistent failure →cardic cirrhosis
VO	M	60	174	63	1.75	0	0	+	Both bases	Ant. transmural	110	-	Increased veins in upper lobes	-
WA	M	44	185	94	2.19	0	slight	+	Both bases	Inf. lateral transmural	456	1150	Pulmonary vascular congestion	-
STE	F	64	164	88	1.95	0	0	0	Both bases	Ant. transmural	210	-	Pulmonary vascular congestion	-
DU	F	66	155	62	1.60	0	+	+	Both bases	Inf. transmural	92	-	Pulmonary oedema	-
HA	M	49	165	64	1.70	0	++	++	Widespread crepitations	Ant. transmural	142	-	Pulmonary oedema	Improved temporarily but died 3 days later +
FI	M	68	167	60	1.67	0	+	++	Both bases	Ant. transmural	120	-	Pulmonary vascular congestion	Hypotensive chronic bronchitis
TA	F	72	158	63	1.64	0	++	++	Widespread crepitations	Ant. transmural	58	-	Pulmonary oedema	IPPV but died Multiple emboli +

TABLE 5

SHOCK COMPLICATING ACUTE MYOCARDIAL INFARCTION

	SEX	AGE	HT.	WT.	S.A.	PAIN	DYSPNOEA	JVP	LUNG CREPITATIONS	E.C.G.	SERUM ENZYMES SGOT	SERUM ENZYMES SCPK	CHEST X-RAY	COMMENTS
TU	F	62	170	67	1.76	O	O	+	Both bases	Post-lateral intramural	150	-	Pulmonary vascular congestion	Survived Shock state + Renal failure Died after 2nd infarct.
PL	M	45	173	73	1.85	O	O	+	Both bases	Antero-lat. transmural	110	-	Pulmonary vascular congestion	Little response to therapy + Died 24 hours later.
LA	M	42	169	68	1.77	+	O	+	Both bases	Anterior transmural	150	-	Not done	Died 3 hours + after admission.
LI	M	54	150	54	1.47	+	O	+	O	Antero-septal transmural	86	-	Pulmonary oedema	Little response to therapy + Died 14 hours later.
AI	M	65	159	68	1.70	O	O	O	O	Anterior transmural	74	-	Pulmonary oedema	Died 3 hours + after admission
ALE	M	72	165	67	1.72	+	O	++	Both bases	Inf. transmural	140	-	Pulmonary vascular congestion	No response to therapy + Died 4 hours after admission.
TA	F	72	158	63	1.64	O	O	+	Scattered crepitations	Ant. intramural	58	-	Pulmonary vascular congestion	Survived shock state + severe LVF.

KEY: Ht. in cms.

Wt. in Kgs.

+ Died

S.A. = Body Surface Area in Squ.m.

TABLE 6

AUTOPSY FINDINGS IN SHOCK AND LEFT VENTRICULAR FAILURE

PATIENT	LVF/SHOCK	HEART WEIGHT	EXTERNAL APPEARANCES	OLD ISCHAEMIC DAMAGE	RECENT ISCHAEMIC DAMAGE	VESSELS			OTHER FEATURES
						A	C	R	
HA	LVF	420	-	Postero-lateral infarct	Infero-septal	-	-	Ath	-
TA	Shock →LVF	350	Normal	-	? Ant. infarct	-	Ath	-	-
TU	Shock →Renal Failure	375	Haemorrhagic softened inf. wall	-	Extensive postero-lateral recent extension	-	Ath T	-	Acute tubular necrosis
PL	Shock	750	Left ventricular hypertrophy	Postero-lateral infarct	Concentric transmural	-	-	-	Chronic bronchitis
LI	Shock	360	Fibrous pericarditis inf. wall	Extensive inferior infarct	Infarction of anterior and septal walls	T	-	-	-
AI	Shock	400	-	-	Extensive antero-septal	T	T	-	-
ALE	Shock	490	Haemorrhagic softened inf. wall	Anterior infarct	Transmural inferior	-	-	Ath	Anaplastic Ca R. middle bronchus

KEY: Heart weight in gms.

A Anterior descending

C Circumflex

R Right coronary

Ath - Rupture of atheromatous plaque

T - Thrombosis

TABLE 7

UNCOMPLICATED MYOCARDIAL INFARCTION

Patient	Systemic arterial pressure (mm.Hg)			Cardiac output ($l.min.m^2$)	Heart-rate (beats/min.)	Stroke volume ($ml.m^2$)	Systemic vascular resistance ($dyne\text{-}sec.cm.^{-5}m^2$)	Pulmonary arterial mean pressure (mm.Hg)	Right atrial mean pressure (mm.Hg)	Arterial Blood				Mixed venous blood oxygen saturation	Oxygen capacity	A-V diff. vols.%
	Systolic	Diastolic	Mean							PaO_2	$PaCO_2$	pH	SaO_2			
AD	119	91	103	2.67	85	31	3020	12	0	69	40	7.42	94	59	20,95	7.33
McW	160	65	104	2.56	80	32	3190	13	3	62	30	7.52	94	63	24.70	7.66
LE	222	122	164	3.28	70	48	3860	18	5	85	48	7.52	98	-	20.12	-
SH	233	113	155	2.29	74	31	5510	17	1	70	36	7.47	97	64	21.17	7.02
McH	173	98	128	1.96	78	25	5200	-	6	79	34	7.48	96	-	22.02	-
CR	118	63	82	2.71	82	33	2440	19	2	69	28	7.50	96	-	18.26	-
RI	144	87	114	3.11	80	39	2950	16	2	78	36	7.46	96	-	20,75	-
DA	101	66	82	3.05	72	43	2150	23	10	58	38	7.42	91	65	19.11	4.97
WH	139	91	111	2.68	92	29	3420	11	0	58	36	7.49	93	67	21.54	7.61
AR	158	89	117	2.55	87	29	2740	22	5	80	35	7.46	96	61	19.96	6.98
McL	136	72	95	2.56	95	26	3010	18	2	65	32	7.49	95	56	21.82	8.51
TH	132	77	101	2.12	84	26	4000	-	0	80	36	7.50	97	-	18.58	-
ST	112	64	84	2.63	60	44	2600	-	9	66	40	7.38	92	-	19.73	-
DI	125	81	97	2.82	80	35	2760	20	11	57	40	7.40	89	75	15.70	2.19
DO	101	65	80	2.68	98	27	2460	28	4	48	41	7.48	87	55	19.13	6.12
SC	121	81	92	2.97	69	42	2660	12	0	67	35	7.44	94	65	19.65	5.70
MU	100	69	82	2.25	87	27	2990	40	5	54	39	7.53	92	48	20.85	9.18
AL	117	81	96	3.02	92	33	2520	24	4	61	46	7.42	92	70	19.45	4.27
HE	117	72	85	3.23	124	26	2080	-	3	42	30	7.40	77	-	26.86	-
RO	119	82	98	2.28	123	18	3390	25	5	58	35	7.43	90	-	21.13	-
FR	105	57	78	3.39	69	47	1930	12	2	78	41	7.40	96	64	18.50	5.92
SO	139	79	104	2.43	80	30	2700	-	7	55	39	7.44	90	-	19.59	-
THO	155	71	104	2.73	77	39	3040	14	2	65	39	7.48	96	-	20.21	-
PE	136	88	109	2.55	96	27	3450	18	4	60	39	7.49	95	68	18.11	4.89
THN	108	23	56	3.42	60	37	2000	-	4	57	36	7.51	92	-	17.51	-
FL	148	71	102	2.64	84	31	3090	24	2	55	38	7.48	91	65	19.09	4.97
Mean	136	78	101	2.71	84	33	3045	19	3.77	64	37	-	93	63	20.17	6.22
S.E.M.	6.54	3.69	4.48	0.075	3.02	1.47	168	1.56	0.59	2.11	0.88	-	0.84	1.7	0.375	0.467
S.D.	33.39	18.83	22.83	0.384	15.39	7.52	859	6.96	2.10	10.77	4.51	-	4.29	6.6	2.21	1.808
N.	26	26	26	26	26	26	26	20	26	26	26	26	26	15	26	15

TABLE 8

LEFT VENTRICULAR FAILURE

Patient	Systemic arterial pressure (mm.Hg)			Cardiac output ($l.min.m^2$)	Heart-rate (beats/min.)	Stroke volume ($ml.m^2$)	Systemic vascular resistance (dyne-sec. $cm.^{-5} m^2$)	Pulmonary arterial mean pressure (mm.Hg)	Right atrial mean pressure (mm.Hg)	ARTERIAL BLOOD				Mixed venous blood oxygen saturation	Oxygen capacity	A-V diff. vols.%
	Systolic	Diastolic	Mean							PaO_2	$PaCO_2$	pH	SaO_2			
CO	84	50	61	1.58	104	15	3110	23	10	47	26	7.49	86	34	17.63	9.25
HO	162	98	118	2.27	68	33	4160	28	4	59	31	7.53	94	53	19.92	8.17
SL	105	69	82	2.79	118	24	2330	38	8	45	41	7.35	78	45	21.32	9.18
VO	117	62	88	2.38	75	32	2920	27	8	59	40	7.47	92	58	19.73	6.71
WA	120	75	85	1.86	120	15	4140	20 (PAw 12)	6	56	37	7.42	90	48	20.13	8.45
STE	96	46	65	1.72	69	25	3020	20 (PAw 10)	5	52	50	7.33	84	56	18.90	5.29
DU	118	62	79	2.74	73	37	2300	26	7	60	47	7.36	90	55	17.67	6.18
HA	80	61	67	1.29	112	12	4150	38 (PAw 30)	12	73	42	7.34	97	29	18.56	12.6
FI	156	94	125	2.12	107	20	4710	24	15	56	58	7.43	90	-	18.53	-
TA	122	44	60	2.17	112	19	2200	32	8	31	28	7.53	64	32	15.54	4.98
Mean	116	66	83	2.09	96	23	3304	27.6	8.3	54	40	-	86.5	46	18.79	7.87
S.E.M.	8.57	5.86	7.17	0.154	6.86	2.70	290	2.08	1.04	3.52	3.18	-	3.02	3.74	0.513	0.796
S.D.	27.11	18.54	22.68	0.486	21.04	8.53	917	6.57	3.30	11.14	10.04	-	9.54	11.22	1.621	2.388
N.	10	10	10	10	10	10	10	10	10	10	10	10	10	9	10	9

TABLE 9

SHOCK COMPLICATING MYOCARDIAL INFARCTION

Patient	Systemic arterial pressure (mm.Hg)			Cardiac output ($l.min.m^{2}$)	Heart-rate (beats/min.)	Stroke volume ($ml.m^{2}$)	Systemic vascular resistance ($dyne\text{-}sec.cm.^{-5}m^{2}$)	Pulmonary arterial mean pressure (mm.Hg)	Right atrial mean pressure (mm.Hg)	AIR	60% OXYGEN						
	Systolic	Diastolic	Mean							PaO_2	paO_2	pCO_2	pH	SaO_2	$\bar{S}vO_2$	Oxygen capacity	A-V diff. vols.%
TU	82	49	63	1.55	84	18	3250	22	3	33	52	52	7.26	80	52	17.41	4.87
PL	55	31	41	1.18	120	10	2600	-	9	74	195	41	7.31	99	-	18.66	-
LA	62	40	49	1.48	110	13	2920	29	9	45	84	39	7.23	93	35	23.32	13.53
LI	59	41	47	1.20	74	16	3320	31	11	67	210	27	7.27	100	34	20.05	13.23
AI	112	85	94	1.20	122	10	6730	24	6	32	61	51	7.26	87	46	20.10	8.24
ALE	52	35	40	1.40	96	15	2280	34	11	60	145	37	7.33	99	38	19.45	11.86
TA	75	47	55	1.36	107	13	3230	26	8	66	128	19	6.95	79	32	15.54	7.31
Mean	71	47	56	1.34	102	13.5	3475	28	8	54	125	38	-	91	40	19	9.84
S.E.M.	7.96	6.78	7.08	0.055	6.83	1.13	560	1.84	1.08	6.46	23.72	4.52	-	3.43	3.20	0.92	1.447
S.D.	21.05	17.95	18.72	0.148	18.06	2.99	1490	4.50	2.85	17.10	62.77	11.96	-	9.07	7.84	2.43	3.55
N.	7	7	7	7	7	7	7	6	7	7	7	7	7	7	6	7	6

THERAPY IN CARDIOGENIC SHOCK

PATIENT	DIGOXIN	THAM.	$NaHCO_3$	5% Laevulose
1. TU	0.75 mg.	100 m.equ.	-	200 ml.
2. PL	1.0 mg.	-	240 m.equ.	400 ml.
3. AI	0.75 mg.	100 m.equ.	-	-
4. LA	1.0 mg.*	-	120 m.equ.*	400 ml.
5. LI	0.75 mg.	-	240 m.equ.	400 ml.

* given prior to study

TABLE 10

TABLE 11

PERSONAL CHARACTERISTICS OF PATIENTS TREATED WITH MORPHINE

NO.	PATIENT	SEX	AGE	HT. (cm)	WT. (kg)	S.A.	PAIN	E.C.G.	SGOT
1	DA	M	48	168	76	1.86	0	high lat. transmural	58
2	WH	M	59	182	93	2.12	0	ant. transmural	98
3	AR	M	53	168	78	1.88	0	inf. transmural	62
4	McL	M	77	178	70	1.86	0	inf. transmural	66
5	DI	M	52	173	67	1.79	0	antero lat. transmural	100
6	FR	M	42	168	65	1.73	0	ant. intramural	53
7	TH	F	43	153	81	1.79	0	antero lat. transmural	98
8	ST	M	62	165	66	1.71	0	inf. transmural	76
9	SO*	M	61	169	68	1.80	0	ant. transmural	100
10	PE*	M	58	167	67	1.75	0	ant. transmural	78
11	THO*	M	64	163	70	1.75	0	inf. transmural	66

* These patients were pretreated with cyclizine

TABLE 12

MEAN CIRCULATORY CHANGES FOLLOWING MORPHINE (10 mgs.) IN 8 PATIENTS WITH ACUTE MYOCARDIAL INFARCTION. (±S.E.M.).

	CONTROL	5 MINS.	10 MINS.	20 MINS.	30 MINS.	50 MINS.
Mean Arterial Pressure mm.Hg.	94.8 (±5.65)	90.7 (±6.88)	91.8 (±6.06)	94.4 (±6.23)	95.5 (±4.99)	97.5 (±4.81)
Cardiac Output $L.min.m^2$.	2.59 (±0.098)	2.77 (±0.155)	2.65 (±0.157)	2.50 (±0.127)	2.58 (±0.111)	2.61 (±0.116)
Heart Rate beats. min.	80.6 (±4.05)	83.8 (±5.07)	84.7 (±3.72)	80.0 (±5.38)	80.3 (±5.38)	81.8 (±4.62)
Stroke Volume $ml.m^2$.	33.0 (±2.52)	33.6 (±2.00)	32.7 (±2.37)	31.9 (±1.93)	33.0 (±2.22)	32.9 (±2.22)
Systemic Vascular Resistance Dynes.sec.cm^{-5} m^2	2950 (±196)	2405 (±192)	2752 (±221)	3008 (±207)	2938 (±134)	2988 (±174)
Pulmonary Arterial Pressure mm.Hg.	20.2 (±2.21)	21.8 (±2.44)	22.5 (±2.68)	22.5 (±2.17)	22.5 (±2.79)	22.0 (±2.86)
Right Atrial Pressure mm.Hg.	5.6 (±1.59)	6.0 (±1.38)	4.6 (±1.55)	6.4 (±1.41)	5.3 (±1.99)	5.3 (±1.66)

TABLE 13

CHANGES IN MEAN ARTERIAL PRESSURE FOLLOWING MORPHINE AND HEROIN

Patient No.	Control	Time (Minutes) 10	20	30	45
MORPHINE	mm Hg				
4	105	96	96	97	98
5	76	71	73	73	73
8	96	90	96	93	91
9	89	82	80	79	76
10	55	46	51	50	56
11	123	100	98	105	100
14	70	61	64	62	60
16	67	65	63	65	67
17	113	93	98	102	105
21	88	87	90	90	73
22	84	91	83	79	75
23	90	82	82	85	82
26	64	68	68	68	66
27	142	125	112	116	116
Mean	90.14	82.64	8.243	83.14	81.29
S.E.	± 6.48	± 5.24	±4.57	± 4.97	± 4.82
S.D.	±24.26	±19.60	±17.08	±18.60	±18.03
n.	14	14	14	14	14
HEROIN					
1	67	65	66	65	66
2	78	83	78	79	75
3	88	82	77	76	75
6	99	94	96	96	97
7	97	99	108	102	96
12	93	100	100	92	93
13	76	78	77	71	70
15	88	80	86	88	88
18	68	68	70	70	70
19	112	105	102	101	101
20	110	89	90	93	98
24	78	70	76	83	82
25	94	75	77	76	75
Mean	88.31	83.69	84.85	84.46	83.54
S.E.	± 4.0	± 3.58	± 3.67	± 3.62	± 3.45
S.D.	±14.45	±12.90	±13.22	±13.06	±12.43
n.	13	13	13	13	13

TABLE 14

CHANGES IN HEART RATE FOLLOWING MORPHINE AND HEROIN

Patient No.	Control	Time (Minutes)			
		10	20	30	45
MORPHINE	beats/min				
4	98	104	103	106	103
5	78	81	83	79	81
8	103	102	103	101	99
9	56	58	58	54	56
10	68	66	68	68	66
11	74	82	81	77	77
14	71	73	70	75	69
16	79	79	77	74	77
17	79	79	77	78	77
21	67	71	67	66	67
22	88	93	91	92	88
23	48	51	51	49	49
26	80	77	78	78	76
27	104	99	96	96	96
Mean	78.0	79.6	78.7	78.0	77.2
S.E.	± 4.3	± 4.2	± 4.1	± 4.3	± 4.1
S.D.	±16.3	±15.8	±15.6	±16.4	±15.6
n.	14	14	14	14	14
HEROIN					
1	67	65	66	65	62
2	61	65	60	60	58
3	84	86	86	84	84
6	93	96	96	92	94
7	65	72	65	66	59
12	65	66	64	64	62
13	67	68	66	64	60
15	58	56	56	58	58
18	76	77	76	73	73
19	89	88	91	89	89
20	77	91	74	91	87
24	72	70	68	70	71
25	71	64	68	71	68
Mean	72.6	74.2	72.0	72.6	71.1
S.E.	2.9	3.4	3.3	3.3	3.6
S.D.	10.7	.2.2	12.1	12.1	13.0
n.	13	13	13	13	13

TABLE 15

CHANGES IN ARTERIAL OXYGEN TENSION FOLLOWING MORPHINE AND HEROIN

Patient No.	Control	Time (Minutes) 10	20	30	45
MORPHINE	mm Hg				
4	57	54	57	57	56
5	52	47	55	47	54
8	62	55	55	53	51
9	75	69	61	69	66
10	67	69	67	63	61
11	68	49	55	63	66
14	60	57	56	54	60
16	65	70	66	61	63
17	69	55	58	62	64
21	62	60	62	65	63
22	63	68	67	68	65
23	76	76	73	75	78
26	76	74	67	68	66
27	54	53	56	68	62
Mean	65.00	61.14	61.07	62.35	62.5
S.E.	±2.04	±2.56	±1.59	±2.00	±1.72
S.D.	±7.64	±9.58	±5.95	±7.50	±6.45
n.	14	14	14	14	14
HEROIN					
1	49	43	47	48	43
2	65	53	68	61	69
3	51	44	53	50	52
6	51	49	49	47	56
7	65	55	61	60	-
12	56	52	53	55	53
13	62	60	63	78	67
15	57	54	54	62	47
18	57	55	57	57	54
19	56	51	51	58	53
20	63	39	45	43	48
24	64	65	65	76	65
25	75	53	58	57	57
Mean	54.15	51.77	55.69	57.84	55.33
S.E.	±2.02	±1.93	±1.96	±2.86	±2.33
S.D.	±7.28	±6.95	±7.08	±10.30	±8.08
n.	13	13	13	13	12

TABLE 16

CHANGES IN PCO_2 FOLLOWING MORPHINE AND HEROIN

Patient No.	Control	Time (Minutes)			
		10	20	30	45
MORPHINE	mm Hg				
4	35	39	39	39	38
5	35	37	37	41	50
8	35	39	40	40	40
9	39	46	49	49	50
10	37	47	44	47	46
11	44	50	51	52	50
14	42	50	52	51	53
16	45	41	49	54	56
17	32	37	37	35	36
21	38	39	39	39	41
22	39	42	42	42	45
23	45	48	51	51	46
26	42	43	48	47	48
27	42	42	42	39	42
Mean	39.28	42.86	44.29	44.7	45.78
S.E.	±1.11	±1.22	±1.48	±1.63	±1.56
S.D.	±4.16	±4.59	±5.53	±6.09	±5.83
n.	14	14	14	14	14
HEROIN					
1	30	37	36	36	39
2	45	54	49	47	50
3	34	39	38	38	39
6	36	36	39	38	40
7	40	49	46	48	-
12	39	45	46	46	44
13	41	42	48	47	48
15	51	50	59	59	63
18	43	48	48	49	51
19	35	38	40	42	42
20	43	53	55	57	55
24	40	48	50	50	49
25	47	51	52	53	54
Mean	40.31	45.38	46.62	46.92	47.83
S.E.	±1.58	±1.75	±1.90	±1.97	±2.13
S.D.	±5.71	±6.30	±6.85	±7.09	±7.39
n.	13	13	13	13	13

TABLE 17

CHANGES IN $/^{-}_{-}H^{+}_{-}/$ FOLLOWING MORPHINE AND HEROIN

Patient No.	Control	Time (Minutes) 10	20	30	45
MORPHINE	n mol.l				
4	33	37	37	37	37
5	33	37	34.5	36	37
8	32	33	32	32	33.5
9	35	38	39	39	40.5
10	33	37	35	37	37
11	38	40.5	40.5	43	41.5
14	35	37	39	38	36
16	35	33	33	38	37
17	43	46.5	49	49	52
21	34.5	35	34.5	34.5	35
22	36	37	38	38	38
23	38	40.5	40	40	39
26	38	39	39	37	38
27	40	40	40	40.5	42.5
Mean	35.96	37.89	37.89	38.50	38.85
S.E.	$\pm$0.83	$\pm$0.92	$\pm$1.13	$\pm$1.07	$\pm$1.20
S.D.	$\pm$3.10	$\pm$3.44	$\pm$4.24	$\pm$4.00	$\pm$4.50
n.	14	14	14	14	14
HEROIN					
1	33	37	34.5	36	37
2	34.5	40.5	37	35	35
3	35	40	36	36	35
6	35	36	36	35	35
7	37	41.5	40.5	41.5	-
12	33	38	38	37	37
13	30.5	34.5	36	34.5	34.5
15	40.5	40.5	43	46.5	40
18	40	40.5	40.5	40.5	40.5
19	32	34.5	35	35	34.5
20	40.5	47.5	46.5	49	47.5
24	36	40	40.5	40.5	38
25	41.5	45.5	46.5	45.5	44
Mean	36.04	39.75	39.23	39.38	38.17
S.E.	$\pm$1.00	$\pm$1.06	$\pm$1.14	$\pm$1.38	$\pm$1.20
S.D.	$\pm$3.60	$\pm$3.80	$\pm$4.11	$\pm$4.98	$\pm$4.15
n.	13	13	13	13	12

TABLE 18

CHANGES IN ARTERIAL pH FOLLOWING MORPHINE AND HEROIN

Patient No.	Control	Time (Minutes)			
		10	20	30	45
MORPHINE					
4	7.48	7.43	7.43	7.43	7.43
5	7.48	7.43	7.46	7.44	7.43
8	7.49	7.48	7.49	7.49	7.47
9	7.45	7.42	7.41	7.41	7.39
10	7.48	7.43	7.45	7.43	7.43
11	7.42	7.39	7.39	7.36	7.38
14	7.45	7.43	7.41	7.42	7.44
16	7.45	7.48	7.48	7.42	7.43
17	7.36	7.33	7.31	7.31	7.28
21	7.46	7.45	7.46	7.46	7.45
22	7.44	7.43	7.42	7.42	7.42
23	7.42	7.39	7.40	7.40	7.41
26	7.42	7.41	7.41	7.43	7.42
27	7.40	7.40	7.40	7.39	7.37
HEROIN					
1	7.48	7.43	7.46	7.44	7.43
2	7.46	7.39	7.43	7.45	7.45
3	7.45	7.40	7.44	7.44	7.45
6	7.45	7.44	7.44	7.45	7.45
7	7.43	7.38	7.39	7.38	-
12	7.48	7.42	7.42	7.43	7.44
13	7.51	7.46	7.44	7.46	7.46
15	7.39	7.39	7.36	7.33	7.40
18	7.40	7.39	7.39	7.39	7.39
19	7.49	7.46	7.45	7.45	7.46
20	7.39	7.32	7.33	7.31	7.32
24	7.44	7.40	7.39	7.39	7.42
25	7.38	7.34	7.33	7.34	7.35

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CIRCULATORY EFFECTS OF HEROIN IN PATIENTS WITH MYOCARDIAL INFARCTION

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Summary The intravenous injection of morphine for the relief of pain in patients with acute myocardial infarction is known to cause significant, and occasionally severe, hypotension. A standard therapeutic dose (5 mg.) of heroin administered intravenously to eight patients with acute myocardial infarction caused little change in the cardiovascular system. The analgesic and sedative effects of the drug were adequate and no undesirable side-effects were observed. Heroin may be preferable to morphine in the treatment of patients with acute myocardial infarction.

Introduction

THE effective relief of pain and anxiety is an essential part of the treatment of patients with acute myocardial infarction. Morphine has long been the drug of choice for this condition in both hospital and general practice. The *British Medical Journal* (1966a) drew attention to the undesirable side-effects of morphine including the

striking changes which it may induce in the hæmodynamic state. The most important of these is a fall in systemic arterial pressure which may be severe even after small doses of the drug (Thomas et al. 1965). Despite these disadvantages, it was concluded that morphine seemed " likely to retain its important place in the treatment of acute myocardial infarction ". The *British Medical Journal* (1966b) further suggested that heroin should be used in the severely ill patient, but cited no evidence in support of this statement. Douthwaite (1953) suggested that heroin is less likely to give rise to nausea and vomiting. The effects of heroin on the circulation do not seem to have been reported.

We have assessed the effects of intravenous heroin on the circulation as far as could be determined without added risk to patients already in jeopardy as a result of acute myocardial infarction.

Patients and Methods

Clinical Data

We investigated eight patients whose personal characteristics and clinical details are shown in table I. All eight patients had sustained an acute myocardial infarction by World Health Organisation (1959) criteria within the previous 48 hours. One patient (no. 3) was shocked. Three others (nos. 3–5) complained of ischæmic chest pain at the start of the study and one of these felt sick. One patient (no. 4) was in first-degree heart block with intermittent Wenckebach periods. Patient no. 3 had frequent ventricular extra-systoles before and during the study. The others were in normal rhythm although all had occasional ventricular ectopic beats. Two of the patients were on anticoagulant therapy (phenindione) but none had received any other drug within the 12 hours preceding the investigation. No patient had an oral temperature above 99·2°F (37·2°C).

Plan of Investigation

The investigations were carried out with the patients in their own beds in a specially adapted side room of a general ward. The first six patients (nos. 1–6) were studied supine with one pillow supporting the head, and two patients (nos. 7 and 8) were studied with the head of the bed raised 10 degrees above the horizontal plane. Control observations were made in each patient over a period of 20 minutes. 5 mg. of heroin diluted in 10 ml. of saline solution was then injected into the right atrium over a period of five minutes, observations being made during this period and for a further 50 minutes in the first six patients and for 30 minutes in the other two. The electrocardiograph was recorded continuously throughout. Recordings of aortic, pulmonary arterial, and right atrial

TABLE I—PERSONAL AND CLINICAL DETAILS OF PATIENTS

Patient	Sex	Age (yr.)	Surface area (sq. m.)	E.C.G.	Clinical condition	Response to heroin
1	M	64	1·73	Anterior infarction	Uncomplicated	Slept
2	M	56	1·98	Posterior infarction	Restless	Drowsy
3	F	41	1·69	Anterior infarction ventricular extra-systoles	Shocked, pain, nausea	Pain and nausea relieved; clinical condition improved
4	M	52	1·72	Posterior infarction 1° heart-block with intermittent periods of Wenckebach	Pain	Pain relieved; slept
5	F	55	1·72	Anterior infarction	Pain, nausea	Pain relieved; slept
6	F	64	1·81	Anterior infarction	Uncomplicated	Drowsy
7	M	64	1·75	Posterior infarction	Hypotensive	Slept
8	M	79	1·86	Posterior infarction	Uncomplicated	Slept

pressure were interrupted only for sampling of arterial and mixed venous blood. The cardiac output was measured at 5-minute intervals during the control period, 2·5 minutes and 5 minutes after the start of heroin injection and at 5-minute intervals thereafter. Arterial blood was withdrawn at the beginning and end of the control period and at 5, 10, 20, 30, and 50 minutes after the start of injection for estimation of oxygen capacity, oxygen tension (P_aO_2), carbon-dioxide tension (P_aCO_2), and pH. Central venous blood was obtained at the same intervals so that the whole-body oxygen uptake could be calculated by the Fick principle.

Techniques

Aortic pressure was recorded through a 55 cm. nylon catheter inserted percutaneously into the left brachial artery and advanced into the aortic arch. The right atrial pressure was recorded through one lumen of a triple-lumen catheter, the tip of which was advanced into the right atrium from the right basilic vein. A fine nylon catheter was " floated " into the pulmonary artery by the technique described by Bradley (1964). All intravascular pressures were transduced by Statham ' P23Db ' strain-gauge manometers. Cardiac output measurements were made by a standardised indicator dilution technique using indocyanine-green injections into the right atrium and sampling from the aorta through a Waters ' XC 300 ' A cuvette densitometer. Details of these techniques have been described elsewhere (Macdonald, Sapru, Taylor, and Donald 1966, Taylor 1966). The electrocardiograph, intravascular pressures, and dye-dilution curves were displayed continuously on a 17 in. oscilloscope so that any significant change could be detected immediately and suitable action taken without delay.

P_aO_2, P_aCO_2, and pH were measured in a combined cuvette apparatus (Instrumentation Laboratories Inc., Boston, Massachusetts). In our hands, the standard deviation about the regression line for the range of measurements in this study was less than 3 mm. Hg, and pH duplicated to 0·005.

Student's t test was applied to the differences between the mean values during the control period in each patient (nos. 1–6) and measurements recorded at 5, 10, 20, 30, 40, and 50 minutes after the start of injection, the null hypothesis being that the difference would be zero.

Results

Clinical Observations

After the administration of heroin, six patients fell asleep within 15 minutes and remained so for the next hour. The other two felt " pleasantly drowsy ". The pain experienced by patients 3–5 was rapidly relieved. The one patient who complained of severe nausea during the control period fell asleep and, on waking at the end

of the investigation, felt completely well. At no time during the studies did the clinical state of any patient give cause for alarm and no undesirable side-effects were observed.

Circulatory Changes

The sequential changes in the circulatory measurements for each patient are shown in fig. 1. The mean changes for the six patients who were investigated horizontally are shown in fig. 2. The results in this group will be considered first.

Circulatory Changes, Patient Horizontal

Mean aortic pressure.—The mean fall was 5 mm. Hg at the 5th and 10th minutes after the start of injection ($P = < 0{\cdot}05$). Thereafter the pressure returned to and remained at normal levels. This was a consistent trend except in patient no. 6 in whom the mean pressure continued to decline gradually for 30 minutes before returning towards control values. The lowest level in this patient was 16 mm. Hg below the control observations.

Cardiac output.—No significant trend was observed after the administration of heroin. Four patients showed small variable changes, which were of no practical importance. In one patient (no. 6), the cardiac output rose by 0·26 litre per minute per sq. m. and then fell steadily to 0·5 litre per minute per sq. m. below control levels. One patient (no. 4) showed a sustained increase reaching a maximum of 0·56 litre per minute per sq. m. above control levels 30 minutes after the start of infusion.

Systemic vascular resistance.—In the shocked patient (no. 3), there was a small but progressive increase of systemic vascular resistance after the administration of heroin. In the other five patients, it tended to fall slightly but this fall was transient in all except patient no. 4 in whom the systemic vascular resistance was raised (4160 dynes per second per $cm.^5$ per sq. m.) during the control period. The mean change was not significant ($P > 0{\cdot}20$).

Heart-rate and stroke volume.—Heroin had little effect on the heart-rate. Minor variations of less than 10 beats per minute were observed except in patient no. 3. Her heart-rate fell by 16 beats per minute due to a decrease in the number of ventricular extrasystoles. Changes in stroke volume were similarly small and variable ($P > 0{\cdot}50$).

Mean right atrial pressure.—The range of mean right

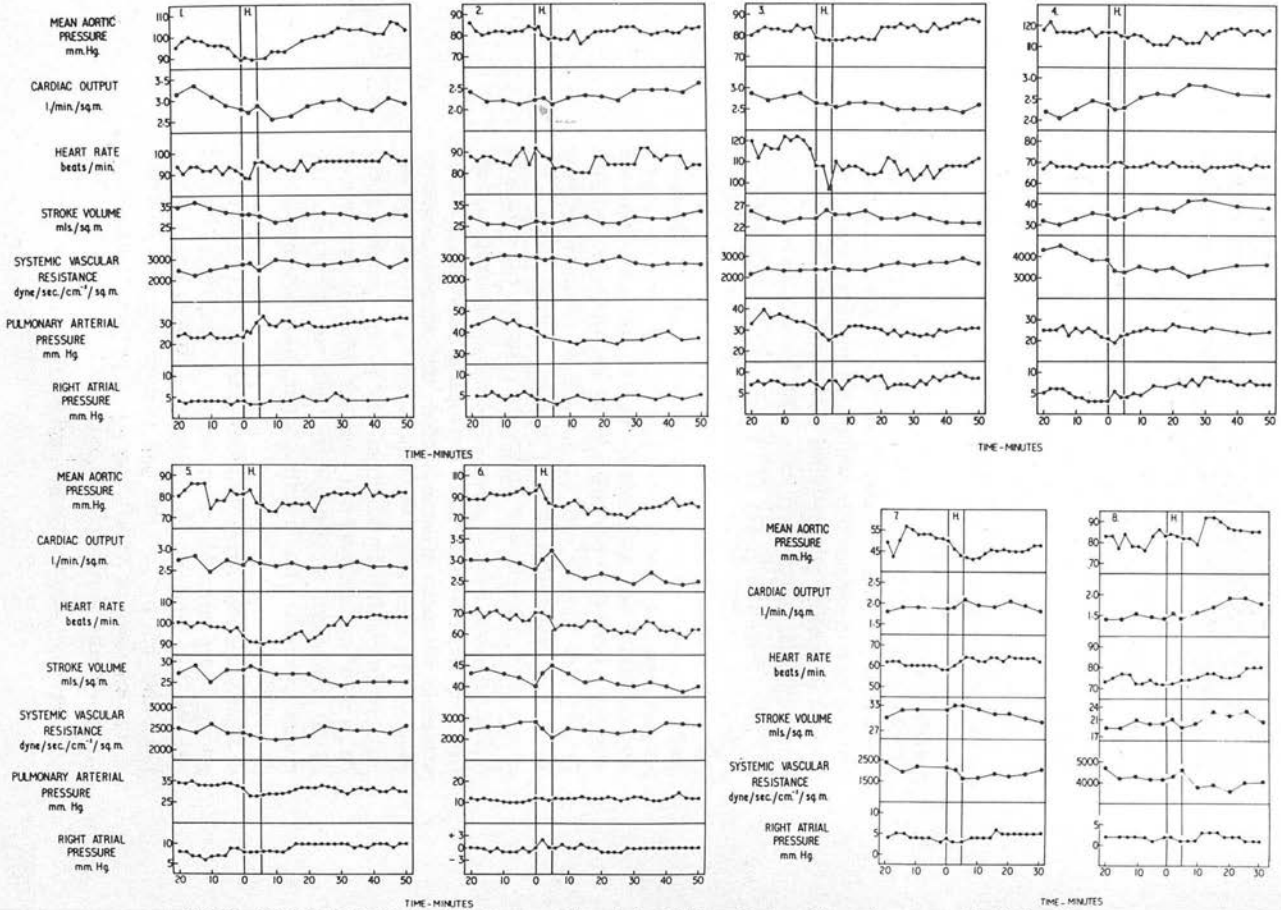

Fig. 1—Circulatory effects of intravenous heroin in eight patients with acute myocardial infarction.

atrial pressure was 4–8 mm. Hg in patients 1–5. In patient no. 6, it was 0 mm. Hg. After the administration of heroin, the mean right atrial pressure tended to rise slightly but in three cases this increase was preceded by a fall of 1–2 mm. Hg in the first 5 minutes of infusion. In only one patient (no. 4) was the change greater than

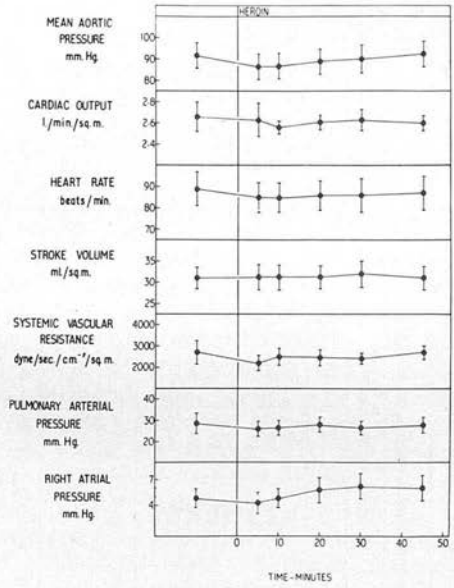

Fig. 2—Mean circulatory changes in six patients with acute myocardial infarction.

2 mm. Hg. The changes for the group were not significant ($P > 0{\cdot}10$).

Mean pulmonary arterial pressure.—The average mean pulmonary arterial pressure was 28·5 mm. Hg (range 23–43 mm. Hg). No consistent trend was apparent after heroin injection. In the three patients (nos. 2, 3, and 5) with the highest mean control pressures of 43, 36, and 33 mm. Hg, respectively, there were decreases of 8, 10, and 5 mm. Hg. Patient no. 1 with a control pressure of 23 mm. Hg showed an increase of up to 8 mm. Hg after the injection, while in the other two patients (nos. 4 and 6) no change was seen.

The mean oxygen uptake, calculated from the cardiac output and arteriovenous oxygen differences, in the

TABLE II—CHANGES IN ARTERIAL OXYGEN AND CARBON-DIOXIDE TENSIONS AND pH AFTER 5 mg. HEROIN

Patient	Oxygen tension (mm. Hg)						Carbon-dioxide tension (mm. Hg)						pH					
	Mean control	Study time (min.):					Mean control	Study time (min.):					Mean control	Study time (min.):				
		5	10	20	30	50		5	10	20	30	50		5	10	20	30	50
1	61	52	52	57	58	54	46	51	56	50	50	50	7·42	7·41	7·39	7·42	7·42	7·42
2	54	54	54	54	54	52	39	37	39	38	38	38	7·53	7·52	7·52	7·52	7·51	7·53
3	45	46	49	54	55	63	41	46	51	51	50	51	7·35	7·34	7·30	7·30	7·34	7·34
4	60	53	46	46	48	55	31	31	37	38	38	37	7·53	7·48	7·46	7·47	7·45	7·46
5	46	38	41	40	45	45	41	50	47	47	47	47	7·48	7·44	7·43	7·42	7·42	7·43
6	69	68	70	66	68	74	35	39	39	38	36	38	7·44	7·42	7·40	7·41	7·44	7·42
7	56	54	53	66	57	66	38	43	47	42	49	45	7·52	7·48	7·46	7·47	7·45	7·46
8	78	69	71	68	73	69	38	39	46	45	38	44	7·52	7·51	7·46	7·46	7·50	7·46
Mean	58·6	54·2	54·5	56·4	57·3	59·8	38·6	42·0	45·3	43·6	43·3	43·8	7·48	7·45	7·43	7·43	7·44	7·44
S.D. (range)	11·1	10·3	10·7	10·1	9·4	9·8	4·4	6·8	6·6	5·4	6·2	5·5	(7·35 −7·53)	(7·34 −7·52)	(7·30 −7·52)	(7·30 −7·52)	(7·34 −7·51)	(7·34 −7·53)
P	..	<0·05	N.S.	N.S.	N.S.	N.S.	..	<0·05	<0·001	<0·01	<0·05	<0·01	..	<0·01	<0·001	<0·01	<0·05	<0·01

control period was 166 ml. per minute per sq. m. (range of 120–200). There was no significant change following the administration of heroin.

Circulatory Changes, Patient Tilted

In patients 7 and 8, the drug was administered while the patient was tilted at an angle of 10 degrees. There were no striking changes in any of the above measurements even in patient 7 who was notably hypotensive.

Arterial Blood-gases and pH (table II)

The mean P_aO_2 of 58·6 mm. Hg (range 45–78 mm.) fell to 54·2 mm. Hg (range 38–69 mm. Hg), within 5 minutes of the start of injection. This decrease, though small, was significant ($P < 0{\cdot}05$). Thereafter, it tended to return to control levels. The mean P_aCO_2 was 38·6 mm. Hg (range 31–46 mm. Hg) in the control period, and was significantly increased in all observations after heroin. The change was greatest 10 minutes after the start of injection when the average P_aCo_2 was 45·3 mm. Hg (range 37–56 mm. Hg) ($P < 0{\cdot}001$). The mean pH was 7·48 (range 7·35–7·53) in the control period and decreased consistently after heroin. The most significant decrease ($P < 0{\cdot}001$) was found 10 minutes after the start of injection when the average pH was 7·43 (range 7·30–7·52).

Discussion

In acute myocardial infarction which is not immediately fatal, the ability of the heart to perform its normal work load and to respond to changes in the demands made upon it is impaired, to a greater or lesser extent. Ideally, any drug which is used to relieve the pain in this condition should not adversely affect the circulation either by increasing the work load of the heart or by decreasing it at the expense of adequate tissue perfusion.

Moor (1930) prescribed intravenous morphine for the treatment of myocardial infarction, and over the years this drug has become standard therapy. Although the analgesic efficacy of morphine is undisputed, its sedative effect is frequently impaired by a tendency to cause distressing nausea and vomiting (*British Medical Journal* 1953, Christie et al. 1958, Dundee et al. 1965). Furthermore, the act of vomiting produces a striking increase in cardiac output and mean aortic pressure (Sapru 1966). These abrupt changes may easily precipitate a crisis in a patient who has only a small cardiac reserve. Heroin is approxi-

mately twice as potent weight for weight as morphine (Reichle et al. 1962, Goodman and Gilman 1965). In equivalent pain-relieving doses, it is reputed to be less nauseating (*British Medical Journal* 1953, Douthwaite 1953). We found the analgesic effect in the three patients with pain was entirely adequate while the sedative effects in all eight patients were excellent. No nausea, vomiting, or other unpleasant side-effects were observed.

Heroin had no dramatic effect on the circulation. The only consistent finding was a small fall in mean aortic pressure in the first 10 minutes after injection. This was of little practical importance and contrasts sharply with the changes after intravenous morphine given to patients with acute myocardial infarction (Thomas et al. 1965). The dosage used in their study ranged from 10 mg. to as little as 3 mg. of morphine. They did not give tables of their measurements but it seems from their diagrams that most of their patients showed significant variations in heart-rate, cardiac output, or blood-pressure, which were independent of the total dose administered.

The precise action of heroin is outside the scope of this investigation which, because of the limited intravascular techniques that can be safely used in patients with acute myocardial infarction, was designed as a practical assessment rather than a pharmacological experiment. However, there is a tendency for the mean aortic pressure, cardiac output, systemic vascular resistance, and right atrial pressure to decrease in the first 10 minutes after heroin injection. These changes, though much smaller and of shorter duration, are the same in direction as those found by Sapru (1966) after injection of morphine. The reason for this quantitative difference between the circulatory effects of the two drugs is not clear. Heroin is rapidly hydrolysed to the active metabolite 6-monoacetyl morphine which is later converted to morphine. It may be that 6-monoacetyl morphine, which passes more rapidly across the blood-brain barrier, has less effect on the circulation. The blood-gas studies show that heroin, like morphine, is a significant respiratory depressant. It seems unlikely that the initial slight decrease in mean aortic pressure could be due to the increase in P_aCO_2 since this remained above control levels throughout the study while the hypotensive effect was transient.

Conclusion

Heroin has provided adequate analgesia and sedation without unpleasant or harmful side-effects and with little effect on the circulation in eight patients with acute myocardial infarction. At a time when the future availability of the drug in the U.K. is once again being debated, these preliminary studies suggest that heroin may be preferable to morphine in the treatments of patients with myocardial infarction.

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